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THE SURVIVAL OF TRANSFUSED ERYTHROCYTES IN HAEMOLYTIC DISEASE OF THE NEWBORN*

BY

P. L. MOLLISON, M.B., M.R.C.P.

(A Report to the Medical Research Council from the S.W. London Blood Supply Depôt)

The survival in vivo of erythrocytes after transfusion to infants has apparently never been studied systematically. In fact, apart from cases reported by Jervell (1924) and Wiener (1943a) in which erythrocytes of a theoretically incompatible group were transfused and found to survive for several weeks, the literature does not appear to contain any records of cases in which the differential agglutination method of estimating the survival of transfused erythrocytes has been applied in an infant. It may be mentioned, however, that Lloyd (1941) has reported two cases in which survival was estimated by the method of resolution of Price-Jones curves.

Acquaintance with the survival time of transfused erythrocytes in normal infants is an essential piece of physiological knowledge. Not only does it provide important evidence of the life of the normal erythrocyte but it also supplies a base line for the comparison of survival in pathological conditions. For this reason alone, a study of the survival of transfused erythrocytes in infants seemed desirable. A further impetus was provided by the recent remarkable discoveries of Levine and his co-workers (1941) in connection with haemolytic disease of the newborn, previously known as erythroblastosis foetalis. These workers have postulated that the essential process in haemolytic disease of the foetus and the newborn is the destruction of the foetal erythrocytes by immune agglutinins formed in the mother's serum, in response to stimulation by an antigen contained in the foetal erythrocytes but not present in the maternal erythrocytes. This theory was supported by observations which showed that in approximately 92 per cent. of cases there was an antigenic difference between mother and foetus with respect to the recently discovered Rh factor. That is to say, in the majority of cases the mother was found to be Rh negative and the father and infant Rh positive. In many cases anti-Rh agglutinins could be demonstrated in the mother's serum. Confirmatory observations have been published by Wiener (1942) and by Boorman, Dodd and Mollison (1942). An obvious inference from these observations is that if the affected infant requires transfusion, Rh-negative blood should be given, since the destructive mechanism may only operate against Rh-positive erythrocytes. Levine et al. (1941, 1942) have mentioned that better results are obtained from the use of Rh-negative blood, and Mollison (1943a) has reported a series of cases in which good results were obtained by using Rh-negative blood for transfusion. Gimson (1943) has also found this treatment strikingly successful. Nevertheless, from observations of red cell counts and haemoglobin values following transfusion, no exact idea of the survival rate of the transfused erythrocytes can be obtained. If the infant's own red cells are being destroyed rapidly at the time of transfusion, the haemoglobin may continue to fall despite transfusion and it is impossible to tell whether the fall is due to destruction of the infant's own erythrocytes or of the donor's erythrocytes or both. Furthermore, if successive transfusions of Rh-positive and Rh-negative blood are given, a better result attending the second transfusion might be due to a spontaneous slowing of the rate of destruction. Only a direct study of the survival rate of transfused erythrocytes of different types can provide the precise knowledge which is desirable.

Quantitative estimation of the survival rate of Rh-positive and Rh-negative erythrocytes in cases of haemolytic disease of the newborn seemed worth while then for the following reasons. Firstly, a demonstration that Rh-positive cells are more rapidly destroyed than Rh-negative cells would provide valuable confirmatory evidence of the correctness of the theory put forward by Levine et alia. Secondly, it should be possible to gain some idea of the length of time after birth for which the active destruction of erythrocytes persists. Thirdly, if the survival rate of Rh-negative cells were found to be constant from one case to the next, suggestive evidence of the life of the transfused erythrocyte in normal newborn infants would be obtained, although this would require to be confirmed by direct study of the normal infant. Fourthly, observation of the difference in survival time between Rh-positive and Rh-negative cells would help to decide how important it is to secure an Rh-negative donor rather than an Rh-positive donor for transfusion in cases of haemolytic disease of the newborn.

The differential agglutination method of estimating the survival of transfused erythrocytes in man was first introduced by Ashby (1919). The method is most simply explained by an example. Blood of group O is transfused to a recipient of

* The substance of these observations was presented in a paper read before the Medical Research Society in October, 1942.

group A. Red cell counts are made before and after transfusion using anti-A serum as a diluent. Whereas before transfusion only a small fraction of cells is unagglutinated, after transfusion the number is increased by the number of group O cells present. Estimations are repeated at intervals until the number of unagglutinated cells has fallen to the pretransfusion level. Unfortunately, when the technique originally suggested by Ashby is used, the number of unagglutinated recipient's cells may often be considerable (say 100,000 per c.mm.). When only 400 to 500 c.c. of donor blood are transfused to an adult, the recipient's unagglutinated cells then form an appreciable proportion of the total number of unagglutinated cells. For this reason the method has been severely criticised and has not been widely used. The method can, however, be very considerably improved. The number of unagglutinated recipient's cells can be reduced by adjusting the strength of the cell suspension used and by employing more potent sera (Jervell) and various other modifications can be made with advantage (Mollison and Young, 1940; Dacie and Mollison, 1943). With these modifications, the number of unagglutinated recipient's cells can often be reduced to 10,000 per c.mm. Moreover, this number is not appreciably increased by agitation of the mixtures. This small number of unagglutinated cells becomes insignificant when large volumes of donor blood are transfused and the method then becomes not only reliable but capable of yielding accurate quantitative results.

One objection to Ashby's original method was that it involved the transfusion of group O blood to recipients of other groups with the attendant possibility of destruction of some of the recipient's erythrocytes by high titre agglutinins in the donor's plasma. This can be overcome to a large extent by removing the bulk of the donor's plasma and using a pooled concentrated red cell suspension prepared from the blood of two donors. If the use of homologous blood is preferred, differentiation can be carried out by means of the anti-M and anti-N sera after choosing a suitable donor (Landsteiner, Levine and Janes, 1928; Wiener, 1934). For instance, blood of group A, type M can be given to a recipient of group A, type N, and the type M cells can be counted in suspensions of blood taken from the recipient after carrying out agglutination with anti-N sera. (The introduction of anti-M and anti-N test sera also made it possible to identify transfused erythrocytes by direct agglutination and some authors have preferred this method. For instance, in the example given above, the type M erythrocytes of the donor could be recognized by being directly agglutinated with anti-M serum in a sample taken from the recipient after transfusion.)

With the discovery of the Rh agglutinogen further possibilities of differentiation have become available.

Using the Ashby method, several workers have estimated the survival of transfused erythrocytes in adults. Ashby herself (1919) obtained irregular results which is not surprising in view of the method used. She did, however, find evidence of survival for periods up to 100 days after transfusion. Wearn, Warren and Ames (1922) also found prolonged survival of transfused erythrocytes (average 83 days) in primary and secondary anaemias. Wiener (1934) using anti-M and -N sera instead of anti-A and anti-B studied the survival in ten 'normal' recipients and found a steady rate of elimination, terminating 80–120 days after transfusion. Dekkers (1939) using a direct differential agglutination method found evidence of survival for an average of 75 days after transfusion, but stated that survival must be longer than the latter figure and might considerably exceed three months. Martinet (1938), using a rather elaborate technique, found evidence of survival for 78 to 108 days after transfusion in six cases. Mollison and Young (1942), using blood stored for periods up to four days in a citrate-glucose mixture, found, in good agreement with Wiener, that the transfused erythrocytes were eliminated at a steady rate and that elimination was not complete until 109 days after transfusion (on the average). Despite the good agreement between workers who have applied the differential agglutination method carefully, it is clear that these results are still not generally known, or if known are not generally accepted as applying to the survival of normal erythrocytes in normal subjects. For instance, in a recent article Baar and Lloyd (1943a) calculated that the life of the erythrocyte was 42 days and made no reference to the fact that this estimate conflicts with the results quoted above.

Cases studied: methods

The survival of transfused erythrocytes was estimated in twenty-one infants affected with haemolytic disease of the newborn of varying degrees of severity. The results of the serological tests made in some of these cases have been reported previously; others are to be reported later (Boorman, Dodd and Mollison, 1942, 1943). One normal newborn infant, one child aged 11 months and one aged 15 months were also studied.

Fresh blood or blood stored for two or three days in citrate-glucose was used in all cases. The amount transfused varied from 50 to 230 c.c. In many cases blood of two serological types (usually Rh positive and Rh negative) was given consecutively or simultaneously, so that the survival of the two types could be directly compared. The transfusions were administered at a drip rate (usually 8 to 15 drops a minute) via the internal saphenous vein. When blood of two different groups was given consecutively a small amount of sodium citrate was run through the cannula intermediately.

Blood samples were obtained by skin prick, using a glass pricker (Wright, 1942), from the warmed heel of the infant, before transfusion, immediately afterwards and then at suitable intervals. In many cases the infant was kept under observation for 4 months or more.

When Rh-positive and Rh-negative bloods were given simultaneously, the following plan was usually adopted. A mixture was prepared from two group O donors, one type N Rh positive, the other type M (or MN) Rh negative. Provided that the infant belonged to type M or MN (as it does in 80 per cent. of cases) and provided that it was Rh positive (as it is in almost every case of haemolytic disease), differentiation of the two types of donor blood could then be carried out with anti-M and anti-Rh sera respectively, for with anti-M serum all but the

type N Rh positive cells would be agglutinated and with anti-Rh serum all but the type M Rh negative cells. Agglutination tests were always carried out on a pre-transfusion sample so that an estimate of the recipient's own unagglutinated cells could be made. In using anti-A, -B or -Rh sera the centrifuge technique described by Dacie and Mollison was used and with anti-M and anti-N sera the technique described by Mollison and Young (1940) was used.

Because of the large amounts of blood used for transfusion the initial concentration of donor cells in the recipient's blood stream usually ranged from 1 to 4 million per c.mm. (average 2·2 million) and was only below 1 million in two instances and above 4 million in two others. Thus survival could be estimated satisfactorily even when the number of unagglutinated cells found before transfusion was as high as 100,000 per c.mm., as it was in a few cases when anti-A or anti-B sera were used. It may be added that in the majority of cases the number of unagglutinated cells attributable to the recipient was below 50,000 per c.mm. As Wiener (1943) has pointed out, the M, N and Rh reactions are more satisfactory in newborn infants, since these agglutinogens, unlike the A and B agglutinogens, appear to be fully developed at birth.

In expressing the results, it is clearly desirable to take as 100 per cent. survival the maximum concentration of donor cells reached in the recipient's circulation after transfusion. In cases in which there was no rapid destruction of the transfused erythrocytes, it was found, as in adults (Mollison and Young, 1942), that the concentration of donor cells was greater in a sample taken twenty-four hours after transfusion than in one taken immediately after transfusion, presumably due to blood volume changes and in several cases the concentration of donor cells in a sample taken later still after transfusion was even greater. This is perhaps not a surprising observation considering the large volume of many of the transfusions in relation to the size of the infant. For the sake of accuracy it must be added that when the maximum concentration of donor cells is not reached for twenty-four hours or more after transfusion, that this concentration will be slightly lower than the true 100 per cent. because of the small amount of destruction that must occur during this initial period of stabilization of blood volume.

In cases in which destruction of the transfused erythrocytes was rapid, the sample taken at twenty-four hours usually contained a considerably smaller concentration of donor cells than that taken immediately after transfusion. Clearly if destruction is rapid, even a sample taken immediately after transfusion may only contain a proportion of the transfused cells, but in such cases the accurate quantitative estimation of survival will be less important.

Below, the maximum concentration of donor cells found after transfusion has been taken as 100 per cent. in all cases and subsequent counts have been expressed as percentages of this figure.

Results

Cases 1–19. In all these cases a diagnosis of icterus gravis neonatorum was made from the presence of jaundice, anaemia and erythroblastaemia. All these infants were Rh positive, all the mothers were Rh negative and in every case the mother's serum contained anti-Rh agglutinins.

SURVIVAL OF RH-POSITIVE BLOOD (table 1). The survival of Rh-positive cells was estimated in ten of these infants, receiving a total of thirteen transfusions of Rh-positive blood (in one instance the group of the donor blood was not determined, see below). Of these thirteen transfusions, nine were given when the infant was fourteen days old or less and in these nine elimination was complete by the end of ten days after transfusion in all but one case (within three days of transfusion in three instances). In the ninth case, elimination was not complete until approximately thirty days after transfusion. Of the remaining four transfusions of Rh-positive blood, two were given to infants (1 and 11) who had previously received Rh-positive blood and had eliminated it rapidly. In each of these cases the donor cells were eliminated less rapidly on the second occasion (see case 1, fig. 1, for instance). The last two transfusions were given to infants aged 31 and 35 days respectively and in these cases survival was prolonged.

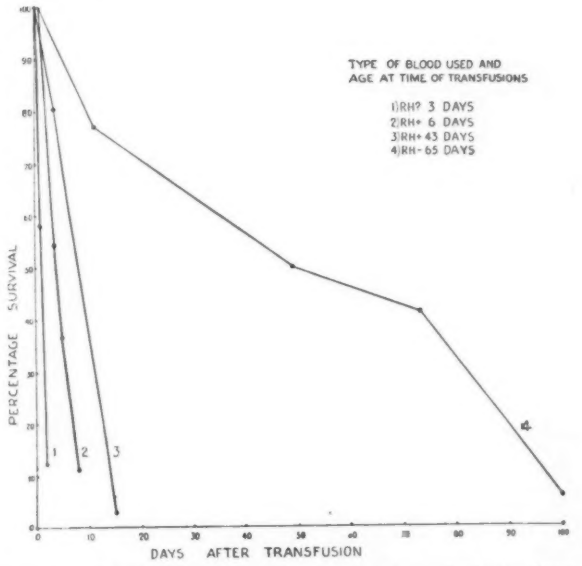

FIG. 1.—Survival of four consecutive transfusions given to an infant (case 1) affected with icterus gravis neonatorum. Second and third transfusions and probably first, Rh positive ; fourth transfusion Rh negative.

Case 1 was of special interest because it received repeated transfusions and because it was studied before the first paper by Levine et alia on the relationship between iso-immunisation and the causation of haemolytic disease of the newborn had become available. Apart from the four transfusions of group O blood whose survivals were estimated (see table 1 and fig. 1) a transfusion of group A blood was given after the second transfusion of group O blood. When the work of Levine and his colleagues was published, all the donors except the first of the five were traced and their Rh groups were determined. It was found that the second and third group O donors were Rh positive, whereas

TABLE 1

SURVIVAL OF RH-POSITIVE AND RH-NEGATIVE ERYTHROCYTES AFTER TRANSFUSION

Case No.	Groups of Infant	Groups of Mother	Age at time of transfusion (days)	Rh-positive transfusions per cent. survival at: Amount given c.c. (ABO group)	7 days	30 days	60 days	Rh-negative transfusions per cent. survival at: Amount given c.c. (ABO group)	7 days	30 days	60 days	Per cent survival at 75 days or more
Cases of Icterus Gravis. Mother Rh negative; Infant Rh positive. Anti-Rh in Mother's Serum												
I	ARh+	ARh−	3	*1*.50 (O)	0	(12 per cent. at 2 days)						
			6	*2*.160 (O)	20	0	—	—	—	—	—	
			43	*3*.155 (O)	72	0	—	—	—	—	—	
			65	—	—	—	—	*4*.120 (O)	87	64	46	6 at 100 days.
II	ORh+	ORh−	9	—	—	—	—	*1*.120 (O)	92	71	54	20 at 88 days.
			10	*2*.100 (O)	61	2	0	—	—	—	—	
III	ORh+	ARh−	8	—	—	—	—	95 (O)	100	80	36	16 at 86 days.
IV	ORh+	ORh−	2	—	—	—	—	*1*.120 (O)	88	50	—	
			35	*2*.50 (O)	90	26	0	*2*.50 (O)	—	—	—	30 at 76 days.
V	ARh+	ARh−	11	*1*.200 (A)	0	0	—	—	—	—	—	
			14	—	—	—	—	*2*.200 (O)	77	—	—	
VI	ARh+	ARh−	14	*1*.50 (O)	0	(39 per cent. at 24 hours)						
			,,	—	—	—	—	*1*.90 (A)	77	60	28	3 at 98 days.
			21	—	—	—	—	*2*.125 (O)	99	48	23	8 at 91 days.
VII	ARh+	ARh−	3	—	—	—	—	150 (O)	—	54	—	
VIII	ARh+	ARh−	14	*1*.60 (O)	0	(at 3 days)		*1*.60 (O)	100	(at 3 days)		
			17	—	—	—	—	*2*.200 (O)	98	73	37	22 at 80 days.
			20	—	—	—	—	*3*.200 (O)				
IX	ARh+	ARh−	3	—	—	—	—	120 (O)	88	78	50	
X	ARh+	ABRh−	5	50 (O)	5	0	—	—	—	—	—	
XI	ARh+	ARh−	9	*1*.90 (O)	12	0	—	*1*.90 (O)	91	—	—	
			17	*2*.100 (O)	79	60	26	*2*.100 (O)	84	65	29	15 at 83 days.
XII	ORh+	ORh−	31	60 (O)	65	49	29	120 (O)	90	67	30	
XIII	ARh+	ARh−	5	*1*.50 (O)	3	0	—	*1*.170 (A)	28	—	—	
			14	—	—	—	—	*2*.200 (O)	83	66	28	
XIV	ARh+	ORh−	18	—	—	—	—	90 (O)	92	73	40	11 at 87 days.
XV	ORh+	ORh−	13	—	—	—	—	300 (O)	100	74	40	2 at 110 days.
XVI	ORh+	ARh−	15	—	—	—	—	100 (O)	96	64	28	
XVII	ARh+	ORh−	18	—	—	—	—	200 (O)	—	—	—	6 at 95 days.
XVIII	ORh+	ARh−	20	—	—	—	—	210 (O)	91	65	34	19 at 78 days.
XIX	ORh+	ORh−	11	—	—	—	—	120 (O)	—	—	—	7 at 97 days.
Case of Icterus Gravis. Mother and Infant ARh+. Anti-Rh_2 agglutinin in Mother's Serum												
XX	ARh+	ARh+	13	60 (A)	73 (9 per cent. at 38 days)	24.5	—	60 (A)	97 (75 per cent. at 38 days)	80	—	
Case of Congenital Anaemia of the Newborn. Mother Rh negative; Infant Rh positive. Anti-Rh in Mother's Serum												
XXI	ARh+	ARh−	4	*1*.115 (O)	94	62	49	*2*.100 (A)	91	69	40	36.5 at 77 days.
Case of acute haemorrhage from the cord in a newborn normal infant												
XXII	ARh+	ORh+	few hours	110 (O)	—	—	—	—	—	76	47	10 at 107 days.
Case of Nutritional Anaemia in a child aged 12 months												
XXIII	ORh+	ORh+	—	120 (O)	95	73	38	120 (O)	96	79	44	35 at 76 days.
Case of Aplastic Anaemia in a child aged 15 months												
XXIV	ARh+	ARh+	—	200 (O)	91	68	40	—	—	—	—	16 at 100 days.

the fourth was Rh negative. Because the first transfusion of group O blood was eliminated even more rapidly than the second, and because in any case Rh positive persons are five times as common as Rh negatives, it is very probable that this first donor was also Rh positive. The group A donor was found to be Rh negative and it was interesting to note from the records that a far more sustained rise in haemoglobin followed this transfusion than either the preceding or following Rh-positive transfusions. Moreover, the jaundice which had remained extreme up to the time of this transfusion completely disappeared during the following three days.

The gradually increasing survival rate of the erythrocytes of successive Rh-positive transfusions is of interest, but it should be noted that Rh-positive erythrocytes were still being eliminated rapidly in this case 43 days after birth.

It will be observed that in the other case receiving successive transfusions of Rh-positive blood (case 11), although the erythrocytes of the first transfusion (given nine days after birth) were rapidly eliminated, those of the second transfusion, given on the 17th day of life, survived very well. The protocol of the tests made in connexion with the first transfusion is set out in table 2.

TABLE 2

SIMULTANEOUS ESTIMATION OF THE SURVIVAL OF RH-POSITIVE AND RH-NEGATIVE ERYTHROCYTES IN A CASE OF ICTERUS GRAVIS NEONATORUM

(Protocol of Experiment in Case 11, First Transfusion)

DONOR BLOOD

Mixture prepared from citrated blood of 2 donors : (1) OMN Rh−, (2) ON Rh+ ; approximately 3 parts (1) added to 2 parts (2)

Control analysis of mixture by agglutination with (1) anti-Rh and (2) anti-M serum

(1) with anti-Rh serum, 3,870,000 free cells per c.mm. (group OMN Rh− cells)

(2) with anti-M serum, 2,690,000 free cells per c.mm. (group ON Rh+ cells)

i.e. mixture contains approximately 3 Rh− erythrocytes to 2 Rh+ erythrocytes

RECIPIENT'S BLOOD GROUP : OM Rh+

	Count of free cells after agglutination with :			
	(1) anti-Rh serum		(2) anti-M serum	
	Total No. of unagglutinated cells	No. of OMN Rh− cells	Total No. of unagglutinated cells	No. of ON Rh+ cells
Before transfusion ..	98,000	—	3,000	—
Immediately after transfusion ..	1,956,000	1,858	1,117,000	1,114,000
1st day after transfusion	(not estimated)		923,000	920,000
4 days after transfusion	2,351,000	2,253,000	277,000	274,000
7 days after transfusion	2,128,000	2,030,000	132,000	129,000
8 days after transfusion	(not estimated)		69,000	66,000

Note that ratio of $\frac{\text{Rh}-}{\text{Rh}+}$ donor erythrocytes in infant's circulation immediately after transfusion approximates quite closely to the 3/2 ratio expected from an analysis of the donor mixture.

It may be mentioned that in one case (case 6) the number of surviving Rh-positive cells found in a sample taken a few hours after transfusion was much smaller (approximately 300,000 per c.mm.) than that expected (approximately 800,000 per c.mm.) compared with the number of Rh-negative cells. Evidently, therefore, a proportion of them had already been destroyed.

SURVIVAL OF RH-NEGATIVE CELLS (table 1 and fig. 2). In eight instances a transfusion of Rh-negative blood was given at the same time as (or within three days of) a transfusion of Rh-positive blood so that the survival of the two types could be directly compared (see table 2, for instance). In all except one of these cases (case 13) prolonged survival of the Rh-negative blood was observed, and even in this exceptional case the survival of the Rh-negative cells was distinctly longer than that of the Rh-positive cells transfused simultaneously (see fig. 3). The survival of a subsequent transfusion of Rh-negative erythrocytes given to this same infant was only slightly below the average for the other cases. In fourteen other instances the survival of transfused Rh-negative cells was estimated. Excluding the first transfusion given to case 13, the average survival rate of Rh-negative cells seven days after transfusion in the eighteen cases in which an estimate was made, was 90 per cent. In sixteen cases survival was estimated thirty days after transfusion and the average figure was found to be 66 per cent. In fourteen cases in which estimations were made at sixty days, the average figure was 36 per cent. In three other cases no intermediate observations were made but an appreciable number of donor cells was recognized in the recipient's circulation 76–97 days after transfusion. In the case of these figures and the figures in table 1 for survival at 75 days or more after transfusion, survival has only been considered ' appreciable ' when the concentration of unagglutinated cells was at least 100,000 per c.mm. greater than the concentration found in a later sample.

Reference to fig. 2 shows that in the majority of cases the survival of the Rh-negative cells was approximately proportional to the time since transfusion, i.e. the curve of elimination, was linear.

In at least two instances, however (case 6, first and second Rh-negative transfusions), the slope of elimination was curved, that is to say, the rate of elimination was at first rapid but then slowed progressively as the concentration of surviving erythrocytes diminished. In three other instances (cases 4, 5 and 7) the initial rate of destruction was distinctly greater than the rate observed in the rest of the cases, but survival was not followed to completion. In case 13, elimination of the erythrocytes of the first Rh-negative transfusion was both rapid and linear.

In a few cases it was observed that a sample taken from the infant a few days after a large Rh-negative transfusion consisted almost exclusively of donor erythrocytes. For instance, in case 8 (A Rh positive) three days after the third transfusion (of Rh-negative blood), the number of O Rh-negative erythrocytes was estimated as 3,940,000 and 3,840,000 with anti-A and anti-Rh serum respectively (allowing for the small number of unagglutinated recipient's erythrocytes), whereas the total count (of O Rh-negative plus A Rh-positive erythro-

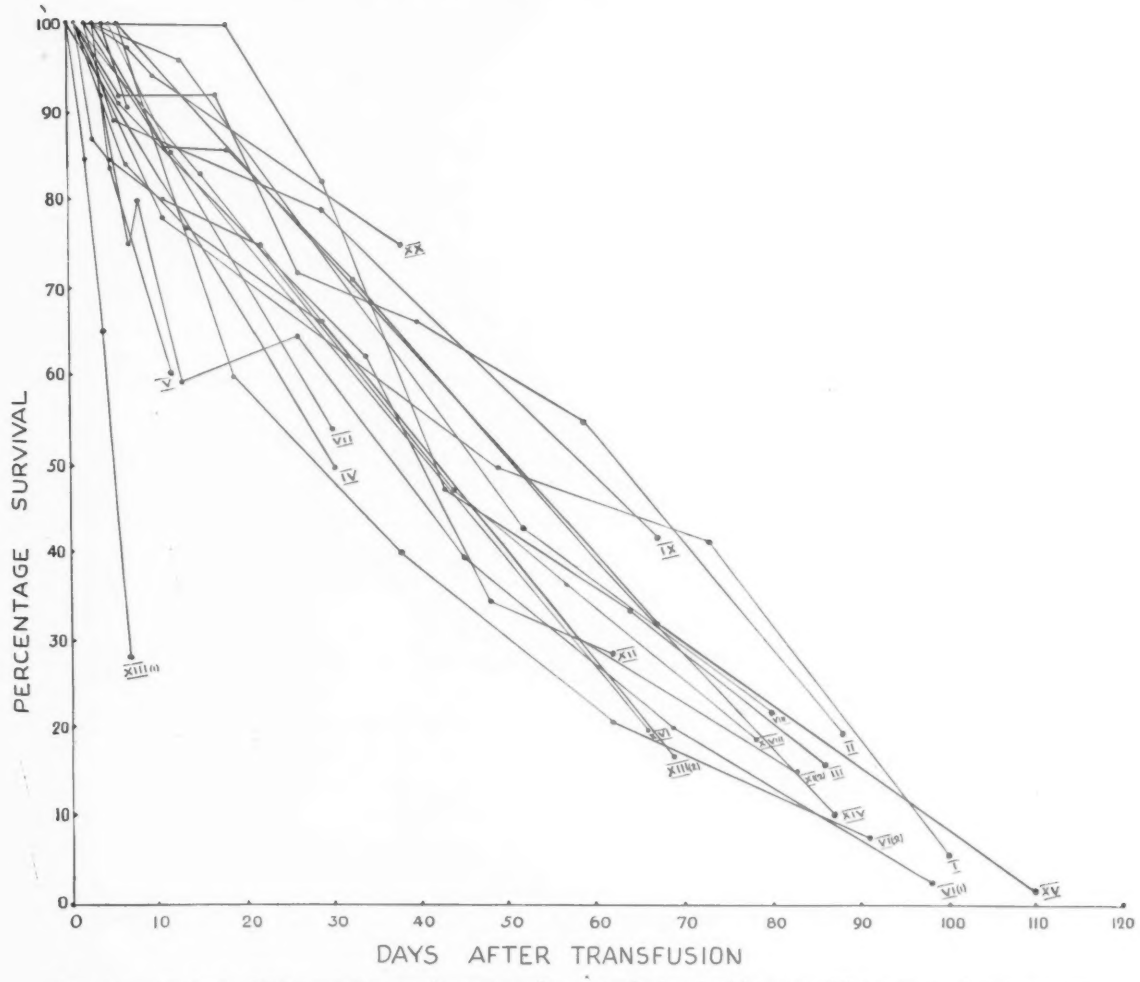

FIG. 2.—Survival of Rh-negative erythrocytes after transfusion in 14 cases of icterus gravis neonatorum (19 separate transfusions)

cytes) was only 4,110,000. The mixtures with anti-A and anti-Rh serum both contained a few small clumps confirming that there were still a small number of A Rh-positive cells present. In case 5 (A Rh positive) a sample taken from the infant twelve days after the O Rh-negative transfusion appeared to contain no A cells at all on testing with anti-A serum.

Case 20. In this case of ' icterus gravis,' although the mother, father and infant were all group A Rh positive, the mother's serum contained an agglutinin active at 37° C. which acted upon the father's and infant's cells and upon approximately 30 per cent. of group O bloods (almost all Rh positive). The serological findings are being described more fully elsewhere* (Boorman, Dodd and Mollison, 1943). This infant was given a transfusion consisting of a mixture of two group A bloods, one of which was agglutinated by the mother's serum and the other of which was compatible with the mother's serum. For convenience, the results have been tabulated as if the first transfusion had been Rh positive and the second Rh negative (see table 1). As shown in the table, an estimate thirty-eight days after transfusion showed that only 9 per cent. of the ' incompatible ' cells contrasted with 75 per cent. of the ' compatible cells ' were surviving.

Case 21. This infant was never jaundiced, but was very anaemic from the time of birth and a diagnosis of ' congenital anaemia of the newborn ' was made; the serological findings were the same as in cases 1–19. As shown in table 1, Rh-positive and Rh-negative erythrocytes transfused on the fourth and fifth days of life respectively both survived for long periods in the infant's circulation.

Case 22. This normal, full-term infant suffered an acute haemorrhage within thirty minutes of birth when the ligature slipped off the umbilical cord. A transfusion was given approximately two hours later. As shown in fig. 4, the survival rate of the transfused erythrocytes was similar to that observed in cases 21, 23 and 24 and survival in this group was indistinguishable from that found in a group of adult recipients (see table 3).

Case 23. This infant, aged eleven months at the time of transfusion, had a history of pallor since the age of two weeks. A blood examination showed: R.B.C. 3,610,000; Hb, 37 per cent.; C.I. 0·5. A blood film showed many megaloblasts, occasional normoblasts and punctate basophilia, polychromasia, poikilocytosis and anisocytosis. A diagnosis of nutritional anaemia was made. A mixture of

* This agglutinin, first called *k*, has been identified as anti-Rh_2; see Wiener, 1943b and Race et al. 1943.

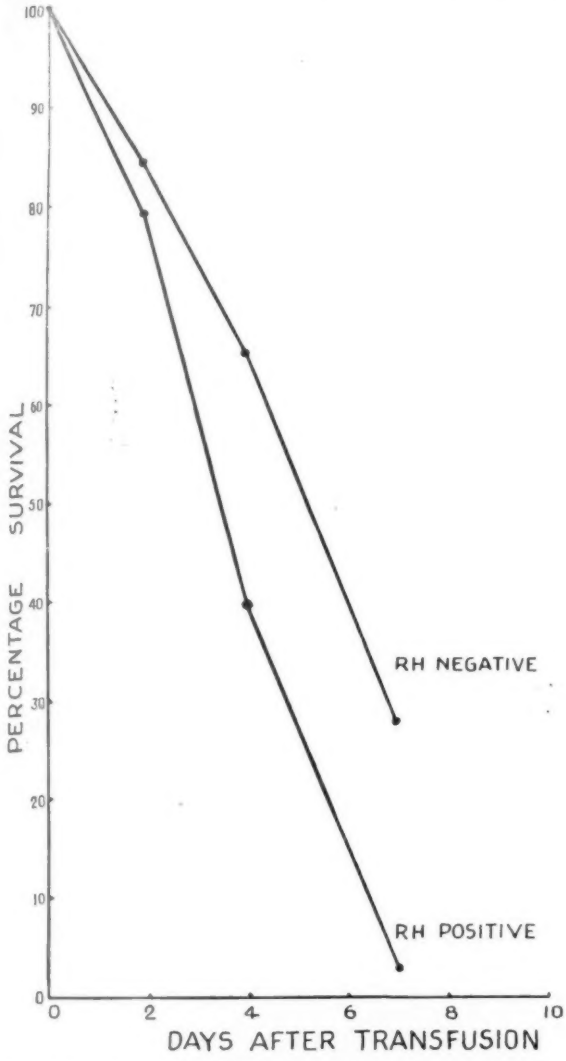

FIG. 3.—Survival of Rh-negative and Rh-positive erythrocytes given simultaneously to a severe case of icterus gravis neonatorum on the fifth day of life. Note rapid destruction of Rh− blood.

TABLE 3

A COMPARISON OF THE SURVIVAL RATE OF TRANSFUSED ERYTHROCYTES (1) IN A GROUP OF 14 ADULTS, (2) IN A GROUP OF 4 INFANTS (AGES : FEW HOURS, 4 DAYS, 12 MONTHS AND 15 MONTHS RESPECTIVELY) NOT AFFECTED WITH ICTERUS GRAVIS NEONATORUM, AND (3) IN A GROUP OF 16 INFANTS AFFECTED WITH ICTERUS GRAVIS NEONATORUM AND TRANSFUSED WITH RH-NEGATIVE BLOOD

Cases	Per cent. survival at		
	7 days	30 days	60 days
(1) Adults	94·4	70·5	41·8
(2) Miscellaneous infants	93·4	71·2	43·0
(3) Infants with icterus gravis (Rh-negative erythrocytes transfused)	90·0	66·0	36·0

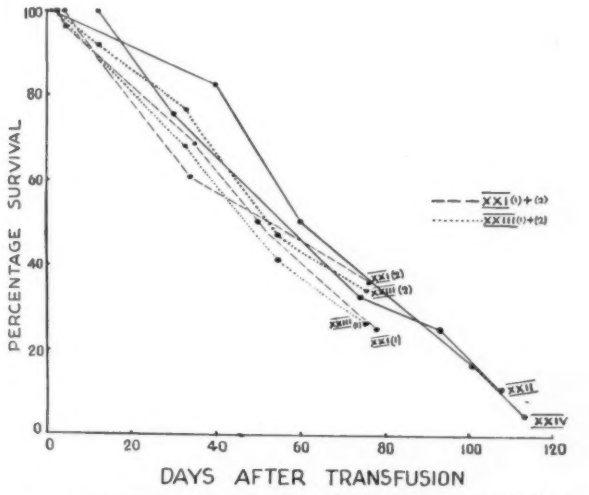

FIG. 4.—Survival of transfused erythrocytes in four infants not affected with icterus gravis neonatorum (cases 21, 22, 23 and 24, see table 1). In cases 21 and 23 Rh-positive and Rh-negative erythrocytes were transfused simultaneously and the survival of the two types is shown.

Rh-positive and Rh-negative erythrocytes was transfused and survival of the two types estimated as a control on the above cases. No appreciable difference between the two was observed and the rate of elimination was approximately 1 per cent. per diem.

Case 24. This child, aged fifteen months, had received many previous transfusions after very full investigations (including marrow biopsy) had established the diagnosis of aplastic anaemia. Again the rate of elimination was approximately 1 per cent. each day.

Clinical observations. It has already been mentioned that in case 1 the jaundice appeared to diminish rapidly after an Rh-negative transfusion. This occurred in case 9 also. This case merits a brief description because of the favourable response that occurred as a result of an early Rh-negative transfusion.

The mother of this infant had had two previous children. The first was healthy at birth but died later from intercurrent disease. The second child died at the age of twelve days from icterus gravis neonatorum. The present infant became jaundiced within forty-eight hours of birth and was found to have a blood picture characteristic of haemolytic disease of the newborn. A transfusion of 120 c.c. of Rh-negative blood was given on the fourth day of life. By the next day the jaundice had faded and it had practically disappeared within forty-eight hours of transfusion. Presumably the filling of the circulation with Rh-negative erythrocytes diminishes the rate of production and, therefore, the rate of destruction of Rh-positive erythrocytes. Although this infant required a further transfusion later, it never looked ill after the first transfusion, and in view of the previous family history it appears that the early transfusion of Rh-negative blood may possibly have been life-saving. The value of this form of treatment is again discussed below.

Discussion

Survival of Rh-positive erythrocytes. It has been shown that during the first fourteen days of life in the majority of cases of 'icterus gravis neonatorum' Rh-positive erythrocytes are far more rapidly destroyed in the circulation than are Rh-negative erythrocytes. Of the cases transfused later than the fourteenth day of life the rate of destruction of Rh-positive erythrocytes was found to have become as slow as that of Rh-negative erythrocytes by the seventeenth day in one case, having been far more rapid between the ninth and sixteenth days; in another case it was found to be still rapid between the forty-third and fifty-eighth days after birth. In two other cases transfused on the thirty-first and thirty-fifth days respectively, survival was distinctly shorter than that of Rh-negative blood in one case, but equally long in the other. In the one case of 'congenital anaemia of the newborn' (case 21) Rh-positive erythrocytes transfused on the fifth day of life were not destroyed any more rapidly than Rh-negative erythrocytes.

It appears from fig. 1 and 3 that when destruction is rapid the slope of elimination is approximately linear as it is in most of the cases in which destruction only occurs slowly, although there are scarcely sufficient points on these graphs to settle the question decisively. Reference to the protocol of case 11 (table 2) suggests that in this case the rate of elimination of the Rh-positive erythrocytes of the first transfusion was proportional to their concentration. For example, the count of donor cells fell from 1,114,000 to 274,000 in the first four days, but only from 274,000 to 66,000 in the next four days. In this case, however, Rh-positive erythrocytes given immediately afterwards in the second transfusion were found to be destroyed slowly, so that a spontaneous slowing of the rate of destruction may have been responsible for the change in rate observed during the elimination of the first transfusion. In haemolytic anaemias in adults it can often be demonstrated that the slope of elimination is not linear but curved, the rate of destruction of transfused erythrocytes being more rapid at first and then becoming slower as the concentration of surviving cells diminishes: types of haemolytic anaemia in which the slope of elimination is linear have, however, been encountered (Brown, Hayward, Powell and Witts, 1943; Mollison, 1943b).

Correlation of the survival time of Rh-positive cells with other features of the cases. In attempting to correlate the rate of destruction of transfused erythrocytes with other criteria of severity, one is faced with the difficulty of obtaining any reliable guide to the latter from clinical or pathological data. For instance, the time of onset of the jaundice is usually regarded as some guide to the severity. Case 6, however, which appeared very ill, became very intensely jaundiced and developed the syndrome of kernicterus, did not become jaundiced until the third day of life, whereas the remaining cases all became jaundiced within the first twenty-four hours of life. In this case the clinical impression of severity was supported by the observation of a short survival time of Rh-positive erythrocytes. Similarly, the degree of anaemia seems quite unreliable as a guide. For instance, in the case just quoted, the haemoglobin had only fallen to 76 per cent. by the fourteenth day. As a contrast, case 21 may be quoted in which the haemoglobin had fallen to 50 per cent. by the fourth day and yet in which an approximately 'normal' survival of Rh-positive erythrocytes was observed. Case 20 is of interest in this connexion. This infant was only moderately jaundiced from the first day of life onwards and the jaundice had practically disappeared by the ninth day of life. The haemoglobin was then 86 per cent., although another estimation on the eleventh day gave a value of 72 per cent. The blood smear showed no nucleated red cells. From the clinical point of view the diagnosis appeared to be doubtful. However, as mentioned above, the mother's serum was found to contain an atypical agglutinin incompatible with the foetal erythrocytes. Moreover, donor blood, also incompatible with the mother's serum, was eliminated quite rapidly as compared with blood that was compatible with the mother's serum. In this case, as in several others in the series, although the haemoglobin had only fallen to approximately 70 per cent. by the tenth day of life, it was found by about the third or fourth week after birth to be as low as 50 to 60 per cent. despite transfusion.

The degree of erythroblastaemia is notoriously unreliable as a guide to severity (Parsons, Hawksley and Gittins, 1933). Case 13, for example, one of the most severe in this series from the clinical point of view, had practically no nucleated red cells in the peripheral blood from the fifth day onwards.

It might be expected that some correlation would be found between the titre of anti-Rh agglutinins in the mother' serum and the rate of destruction of Rh-positive erythrocytes and in fact the highest titres were found in the sera of the mothers of cases 6 and 8 in whose infants the most rapid destruction was observed. This correlation, however, was not found in other cases.

Survival of Rh-negative erythrocytes. As shown in table 3, the survival of Rh-negative cells in the majority of cases investigated is but little different on the one hand from that observed in a small group of infants not affected with icterus gravis neonatorum, and on the other from that found in a group of adults. The fact that the survival rate of transfused erythrocytes in infants appears to be similar to the rate observed in adults does not necessarily imply that the life of the normal erythrocyte is the same in the two, because in each case erythrocytes from adults were transfused and if erythrocytes taken from infants had been transfused instead the results might have been different.

The case (case 13) in which a rapid destruction of Rh-negative cells was found deserves further comment. This infant became jaundiced within a few

hours of birth. It was first seen on the fourth day of life, by which time it had become intensely jaundiced, and it was noted that its stools were pale and its urine dark. The haemoglobin was found to be 76 per cent. and a blood film showed the presence of a few nucleated red cells. The infant's group was A Rh positive, that of its mother A Rh negative and her serum contained weak anti-Rh agglutinins. On the next day a transfusion of 50 c.c. group O Rh-positive blood was followed by 170 c.c. of group A Rh-negative blood, a small volume of sodium citrate solution being run in in between the two to prevent their mixing outside the body. As noted above, a rapid destruction of the group O Rh-positive cells was observed and the destruction of the group A Rh-negative cells was only slightly less rapid.

The diminished survival of the Rh-negative cells in this case might be ascribed to at least three possible causes. (1) Some abnormality of the donor blood. To this it can only be answered that the donor appeared to be normal and that, in a series of survival tests carried out in adults, no similar rapid destruction of cells from an apparently normal donor has been observed. (2) The A cells might have been sensitized by high titre agglutinins introduced in the plasma of the group O blood. The titre of the anti-A agglutinins was determined, however, and found to be only moderate. Moreover, only a small amount of group O blood was transfused. Even after the injection of high titre incompatible agglutinins it is usually impossible to detect them in plasma taken from the opposite arm (Thalhimer 1942). Moreover, in other cases in which this type of experiment has been carried out a similar rapid destruction of the A cells has never been observed. (3) The A ' Rh-negative ' cells may have been ' Rh-positive ' with the mother's serum. It is well known now that some ' Rh-positive ' bloods react with some anti-Rh sera but not with others. The donor blood was, however, tested with seventeen different anti-Rh sera and, more important, with the mother's serum on different occasions and was always negative.

Thus, it seems probable that this infant had the capacity of destroying Rh-negative erythrocytes almost as rapidly as Rh-positive erythrocytes. As noted above, in four other cases the initial destruction of Rh-negative erythrocytes was distinctly more rapid than that observed in the majority of cases. It may be significant that in these cases the transfusion had either been given within the first three days of life (cases 4 and 7), when the destruction of Rh-positive cells was probably proceeding very rapidly, or had been given to an infant in which the destruction of Rh-positive cells is known to have been proceeding very rapidly at the time of transfusion (cases 5 and 6). In case it may appear that the figures from which these deductions are drawn are not outside the limits of experimental error, those for case 5 may be quoted. In this case, the concentration of donor cells immediately after transfusion was 4·8 million per c.mm.; twelve days later, the figure had fallen to 2·9 million per c.mm. If elimination had occurred at the rate of only 1 per cent. per day, as it appeared to in many of the other cases, the count of donor cells on the twelfth day should have been approximately 4·4 million per c.mm. Since the error of this method is similar to that of ordinary blood counting, provided that satisfactory agglutination is secured, it is clear that the figure of 2·9 million is outside the likely error and, therefore, that the rate of destruction must have been greater than 1 per cent. per day in this case.

It thus appears that in some cases, probably those in which the destruction of Rh-positive cells is proceeding very rapidly, that there may be some overlap in the destructive mechanism, so that Rh-negative cells, though not destroyed as rapidly as Rh-positive cells, are destroyed more rapidly than they are in the circulation of the normal infant.

Nevertheless, it seems clear that in the majority of cases Rh-positive erythrocytes are far more rapidly destroyed than Rh-negative erythrocytes in cases of haemolytic disease of the newborn, and thus the theory of destruction by immune specific agglutinins is strongly supported. The observations in case 20 are particularly interesting in demonstrating that it is not Rh-positive erythrocytes as such which are destroyed rapidly, but erythrocytes containing the antigen to which the mother has become sensitized.

Value of transfusions of Rh-negative blood. In an earlier report (Mollison, 1943a) the results of treating cases of haemolytic disease of the newborn with transfusions of Rh-negative blood were referred to and it was pointed out that the favourable recovery rate (seventeen out of seventeen cases transfused) exaggerated to some extent the value of this form of treatment, because the infants transfused included many mild cases that might have recovered without transfusion, whereas the infants that had not been transfused and that died before a transfusion could be given (ten out of ten) included some more severe cases that transfusion might not have saved. Although the value of this form of treatment in the moderately severe cases cannot be doubted, an estimate of its power to save life in the seriously ill cases, that would otherwise die within a few days of birth, will only be possible when the results of treating a large series of the latter are available. As mentioned above, the amount of Rh-positive erythrocytes produced is probably diminished by massive Rh-negative transfusions and this doubtless accounts for the rapid disappearance of jaundice observed in some of the cases. On theoretical grounds, early massive Rh-negative transfusions might, therefore, be expected to lower the incidence of kernicterus.

Further observations. It may be mentioned that variations in the haemoglobin level between one infant and another before and after transfusion did not appear to affect the survival time of the (Rh-negative) erythrocytes.

For instance, in case 15, the red cell count rose to 6,530,000 per c.mm. (Hb 136 per cent.) after

transfusion and six days after transfusion the figures were 6,440,000 per c.mm. and 128 per cent. Nevertheless, the survival time was just as long as in case 14 for instance, in which the haemoglobin never rose above 98 per cent. In two other instances no increased destruction was observed, although the haemoglobin was raised above 110 per cent., namely, case 21 in which the haemoglobin was 130 per cent. one day after transfusion, 118 per cent. six days after and 110 per cent. at thirteen days and case 11, in which the haemoglobin was 114 per cent. after transfusion, 118 per cent. at six days and 110 per cent. at thirteen days.

The observation that no increased rate of destruction occurs when the infant is rendered plethoric (Hb greater than 110 per cent., Haldane) is of some interest in view of the generally accepted theory of physiological jaundice, which is that jaundice results from a physiological process designed to destroy the excessive red cells which, though needed in foetal life, are unwanted after birth. If this theory were correct, it would be expected that an increased destruction would be observed when the haemoglobin was raised above, say, 110 per cent. The following case may be quoted since it demonstrates even more forcibly than the above cases that the infant may tolerate a high haemoglobin level.

A woman who had previously given birth to an infant with icterus gravis neonatorum was delivered of a full-term infant which appeared normal at birth. Nevertheless, as a precaution it was decided to start a drip transfusion of Rh-negative blood while the infant's blood was taken to a laboratory for examination. When it was found that the infant was Rh-negative and evidently normal, the transfusion was stopped, some 80 c.c. having been given. The haemoglobin which had been 134 per cent. before transfusion was raised to over 150 per cent two days later. Ten days after birth the haemoglobin was 134 per cent. These haemoglobin estimations were carried out with a Haldane haemoglobinometer standardized at the National Physical Laboratory. During these ten days the infant never exhibited the slightest tinge of jaundice.

It is difficult to reconcile these findings with the existence in the normal infant of an active destructive mechanism.

Principle of selection of blood donors for infants affected with haemolytic disease of the newborn

When there is time to carry out serological tests upon the mother's and infant's bloods before choosing a donor, it is clear that the principle should be to discover the nature of the immune agglutinin causing the destruction of the foetal erythrocytes and then to select a donor whose red cells lack the corresponding agglutinogen. In most cases this will mean selecting an Rh-negative donor of a compatible ABO group.

Anti-Rh agglutinins occurring in human sera do not give exactly parallel reactions in vitro; in fact it is now apparent that several different varieties occur, evidently corresponding to different subtypes of Rh agglutinogen. For this reason, and because there are certain other difficulties in Rh testing, the erythrocytes of prospective donors should always be tested against more than one powerful anti-Rh serum and at least one of these sera should be of the type that gives the lowest proportion of negative reactions with random human bloods. The most reliable test of all, when the mother's serum contains anti-Rh agglutinins which give good reactions in vitro, is to test the donor's erythrocytes directly against her serum. This direct test becomes essential when the mother's serum contains atypical anti-Rh agglutinins (as in case 20 in this series) or when her serum contains atypical agglutinins unrelated to anti-Rh.

It may be pointed out that in newborn infants, testing of the donor's erythrocytes against the mother's serum is a more desirable precaution as a preliminary to blood transfusion than is direct testing against the infant's serum. This is because for some time after birth the infant's serum only contains agglutinins derived from the mother's serum (see Polayes, Lederer and Wiener, 1929) and because the titre of these agglutinins is on the average about ten times lower in the infant's serum (Wiener and Silverman, 1940). This method of selection, if employed alone, would sometimes lead to the choice of a donor of theoretically incompatible group. For instance, when the mother is group A and the infant O, an A donor would be compatible with the mother's serum, although theoretically incompatible with the infant's serum. However, there is reason to believe that in such cases the donor erythrocytes survive for long periods in the infant's circulation, for at least six weeks in one case (Jervell, 1924) and at least fifty days in another (Wiener, 1943). At the same time it is probably sounder to transfuse blood of a theoretically compatible group until more exact knowledge of the time of development of iso-agglutinins in the infant has been acquired.

For the reasons stated in the preceding paragraph, the use of the mother's erythrocytes, washed free from plasma (Lloyd, 1943), has much to commend it from the theoretical point of view. It is doubtful, however, whether this will often prove the most convenient procedure in practice.

The following case is a reminder that Rh-negative blood of the same group as the infant is not always the most suitable for transfusion.

Infant H., a firstborn male, became jaundiced within a few hours of birth and developed a definite anaemia by the end of the first week of life. It was found that the infant's and father's blood group was B Rh positive, whereas the mother was group O Rh positive and her serum contained tremendously potent immune anti-B agglutinins but no atypical agglutinins. In this case, therefore, it seemed extremely probable that destruction of foetal erythrocytes by anti-B agglutinins was occurring and that group B cells, whatever their Rh group, would be eliminated more rapidly than group O cells. Accordingly, group O blood was used for transfusion—with satisfactory results. This case

again demonstrates the wisdom of testing the donor's erythrocytes against the mother's serum.

In emergency, and when it is impossible to carry out serological tests, group O Rh-negative donors will be found suitable in the great majority of cases. It may be noted, however, that the causation of haemolytic disease of the newborn by an atypical agglutinin Hr acting for preference on Rh-negative bloods has been described (Levine et alia, 1942)* so that in exceptional cases Rh-negative blood may prove unsuitable. However, if the donor cells are tested against the mother's serum, such exceptional cases should be detected.

Summary

(1) In eight out of nine cases of 'icterus gravis neonatorum' transfused during the first fourteen days of life Rh-positive erythrocytes were eliminated from the infant's circulation within ten days of the transfusion. In the ninth case elimination was not complete until thirty days after transfusion. In one further case, in which the destruction of the foetal erythrocytes was due to an atypical anti-Rh agglutinin, erythrocytes containing the corresponding agglutinogen were destroyed rapidly.

In four cases in which Rh-positive erythrocytes were transfused after the fourteenth day of life, destruction was less rapid and in two instances was as slow as that of Rh-negative erythrocytes in two instances.

(2) Rh-negative erythrocytes transfused to twenty-one infants with haemolytic disease survived for not less than approximately eighty days in all but one case. In the majority of the cases the rate of elimination appeared to be uniform, so that approximately 1 per cent. of the erythrocytes was eliminated each day and the total time of survival appeared to be approximately one hundred days. In five instances, however, the initial rate of destruction appeared to be distinctly greater and in the one exceptional case mentioned above only 28 per cent. of the donor cells were found to be surviving seven days after transfusion. Because of the absence of any obvious cause for this more rapid destruction in certain cases, it seems possible that there may be some overlap in the destructive mechanism in this condition, that is to say, it may not always be directed exclusively at Rh-positive erythrocytes.

(3) In one normal infant transfused within a few hours of birth, in one infant aged eleven months and in one aged fifteen months, the survival of transfused erythrocytes was estimated and found to correspond closely with that of Rh-negative erythrocytes in the majority of cases of haemolytic disease of the newborn. This rate of survival is similar to that which has been found in adults, i.e. approximately 1 per cent. of the total number of transfused erythrocytes are eliminated from the recipient's circulation each day after transfusion. In all these experiments blood from adult donors was used for transfusions.

(4) When an infant with haemolytic disease of the newborn has to be transfused, Rh-negative blood of its own group is recommended when serological tests have been made and it is fairly certain that destruction is due to anti-Rh agglutinins. Group O, Rh-negative blood is recommended when no tests have been made and group O blood should be used when destruction is thought to be due to anti-A or anti-B agglutinins. When destruction is due to agglutinins other than atypical anti-Rh, group O blood compatible with the mother's serum is probably the safest. In every case direct matching of the donor erythrocytes against the mother's serum seems a desirable precaution before transfusion.

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* See also Race and Taylor, 1943.

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ADDENDUM

Whilst this paper was in the press, a further article was published by Baar and Lloyd (1943b) in which considerable criticism was directed against the Ashby method, and stress was placed upon the irregular results obtained by Ashby. From an analysis of cell-diameter distribution curves following transfusion and from other studies it was concluded that ' . . . the conception of an " intrinsic " longevity of the red cell is purely relative. . . . ' Finally, it was concluded that ' transfusion experiments . . . are useless for the estimation of the normal life span of the erythrocyte.' There is only room here for the following comments.

Ashby's irregular results have not been confirmed by recent workers who have had the advantage of using improved methods. Contrary to the supposition of Baar and Lloyd, the disappearance curve of transfused erythrocytes, as estimated by the differential agglutination method, in subjects not affected with a haemolytic anaemia, is normally linear and, moreover, almost always extends for about a hundred days after transfusion [see references to Wiener (1934) and to Mollison and Young (1942), and see table 3 in the present paper; see also Brown, Hayward, Powell and Witts (1943)]. These observations strongly suggest, firstly, that the erythrocyte has a normal ' span of life,' and secondly, that this survival time is approximately one hundred days.

SPINA BIFIDA AND ITS ASSOCIATED SKULL DEFECTS

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Some degree of interest has recently been aroused in the question of the occurrence and incidence of spina bifida. Despite the efforts made by many theorists in the past, its mode of production still remains obscure; it is known that fundamentally there is a defective formation of the mesodermal tissues surrounding the primitive neural plate, and that the process of chondrification and subsequent ossification of the early membranous spinal column may lead to the production of a minor fault such as spina bifida occulta, or to a major fault such as myelocele, meningocele, myelomeningocele, or syringocele, but the reasons why this defective development should be brought about are not known.

Earliest opinions ascribed it to supernatural happenings and maternal impressions, a view which lingered on until 1857 when it was mentioned by Wertheim in his report of a case. The first scientific theory was due to Morgagni, and quoted by Alexander in 1769. He suggested that there occurred an increased pressure of the cerebro-spinal fluid, which prevented closure and union of the vertebral laminae, and also gave rise to the frequently associated hydrocephalus. This was disproved by Koch (1881), who pointed out that the pressure of the cerebro-spinal fluid could not exceed that of the surrounding liquor amnii, and also by the London Clinical Society, who appointed a committee to investigate the subject in 1885, which demonstrated that general dilatation of the central canal did not occur as would be expected if the pressure were increased. Other observers considered that there existed a mechanical interference with the nutrition and development of the mesoblast of the spinal region, though they could not agree as to its nature.

St. Hilaire in the early part of the nineteenth century, and Dareste (1882) considered that amniotic adhesions were responsible, but Mall (1905) pointed out that spina bifida was of frequent occurrence in amphibia in whom no amnion is present. Lebedeff (1881) suggested that different parts of the embryo might grow at different rates, thereby producing abnormal curvatures and kinking of the embryonic spine, which might result in maldevelopment of the mesoblast. Similarly, Von Recklinghausen (1886) suggested that there was a primary aplasia of the skeletal axis resulting in the length of the cord exceeding that of the spine, which accommodated itself in the limited space by the process of bending, and so produced a spina bifida. Richter (1888) was able to produce experimental spina bifida by maintaining chick embryos at varying temperatures, thereby proving that external influences could affect the mesodermal development, whilst Morgan and Tsuda (1894) also demonstrated this by immersing frog's eggs in 0·6 per cent. saline. Bland Sutton (1888), by analogy with associated alimentary tract defects, suggested that the cord was a highly differentiated section of the gut, and as an obsolete canal was, therefore, prone to cystic dilatation. Cumston (1903) stated that syphilis was an important cause. Ballantyne (1902) considered that a germinal theory was the correct one, in view of the repeated occurrence of spina bifida in known families and also in twins. The committee of the London Clinical Society also favoured this view.

Good (1910), after an excellent review of past theories, came to the conclusion that in these cases there was an arrested development of the mesodermal tissues from which the spinal meninges were produced, caused by a mechanical agent of unknown nature. Observers now seem to be agreed upon the defective development of the mesoderm, but the main question whether this be due to germinal and hereditary causes, or to an external influence is still unsettled. Fry (1943), in a recent memorandum, reported two cases of spina bifida occurring in binovular twins, and concluded that the cause was basically a developmental anomaly not due to a mechanical agent nor to an external influence.

The majority of cases of spina bifida appear sporadically in apparently healthy individuals and families, but some examples are recorded in which the features of a familial incidence can be discerned. Butler-Smythe (1889) recorded a family of five, in which three children suffered from spina bifida associated with hydrocephalus, whilst the remaining two had hydrocephalus alone. Pybus (1921) described a family of four children who exhibited respectively spina bifida and hydrocephalus, spina bifida occulta, lumbo-sacral meningomyelocele, and a large coccygeal dimple, whilst there has recently

been recorded a family of seven children of whom five were afflicted with the defect. These instances in the literature are rare, and yet when they do occur they do not appear to be the result of mere coincidence.

Attempts to ascertain the hereditary features of this anomaly have in the past yielded few results. This is largely due to the fact that cases exhibiting spina bifida rarely live and rarely reproduce, so that the defect has not the opportunity to be handed down from parent to child. The few cases that do have offspring are merely the cases of spina bifida occulta and the rare cases of successful operation that live on to adulthood, and when their children are born their original defect is not known, or is overlooked, and the hereditary incidence, if any, is not observed. Owing to the paucity of such cases and the number of years that must elapse prior to parenthood, the laws governing the inheritance of spina bifida are not likely to be elucidated by research directed along these channels. Similarly, the examination of the parents and siblings of known cases of spina bifida only rarely produces evidence of other related cases, and has provided insufficient material for the formulation of laws of heredity. It is apparent that if these laws are to be discovered, some other method in which more frequent and non-fatal examples abound will be more conducive to success.

Skull defects

This alternative method is provided by the study of the skull defects which may occur in association with spina bifida. These defects, presently to be described, are caused by a process analogous to that which causes spina bifida, and so may provide a clue to its mode of formation; moreover they occur more frequently than spina bifida, at an actual rate of 0·94 per cent. of all births, and they may occur in normal individuals, so that they provide much more material for the study of their inheritance.

These defects, which promise so much, are the maldevelopments of the cranial vault bones, which we have recently named craniolacunia and craniofenestria (1943a). These conditions were originally described in this country by West (1875), but they have since been overlooked. Thus Pybus (1921) in his report, gives a list of congenital malformations associated with spina bifida, but makes no mention of the cranial vault bones. Good (1910) devotes six pages to descriptions of associated defects, but does not include these anomalies, although he refers to rarer ones, such as splitting and complete absence of the occipital bone; whilst Fry (1943) makes no mention of any associated skull defects.

These conditions occur most frequently in cases of spina bifida, but are also encountered in association with hydrocephalus, craniostenosis, encephalocele, talipes, defective rib formation, and maldevelopment of the face, as well as in otherwise normal cases. In the same manner as spina bifida, they occur in mesoderm surrounding nervous

FIG. 1.—Radiograph of skull at birth showing craniolacunia.

tissue and affect these cranial vault bones, which are developed from membrane. Craniolacunia consists of an irregular ossification of the inner surfaces of the bones whereby thick bony bars or ridges are produced, which branch and unite in such a way as to form a reticulated pattern of circles and ellipses. In between the bars exist thinned areas of bone, which form the lacunae from which the condition is named (fig. 1, 3 and 4). In craniofenestria the defective ossification is carried a stage further, and areas marked by absent bone formation occur between the bars, so producing a pattern of fenestration (fig. 2, 5 and 6). In craniolacunia the outer surfaces of the bones are normal, as they are also in craniofenestria between the actual areas of absence of bone formation. The bones affected may be the frontals, parietals, great wings of the sphenoid, squamous temporals and the squamous occipital, and the deposition of bony tissue may be so deficient as to reduce the weight of the bones by

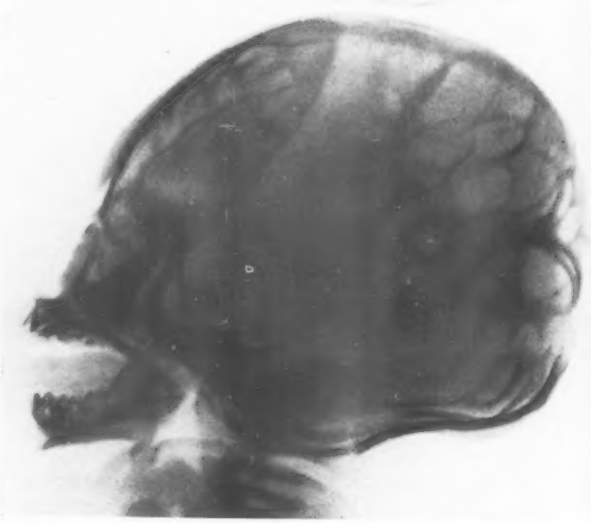

FIG. 2.—Radiograph of skull at birth showing craniofenestria.

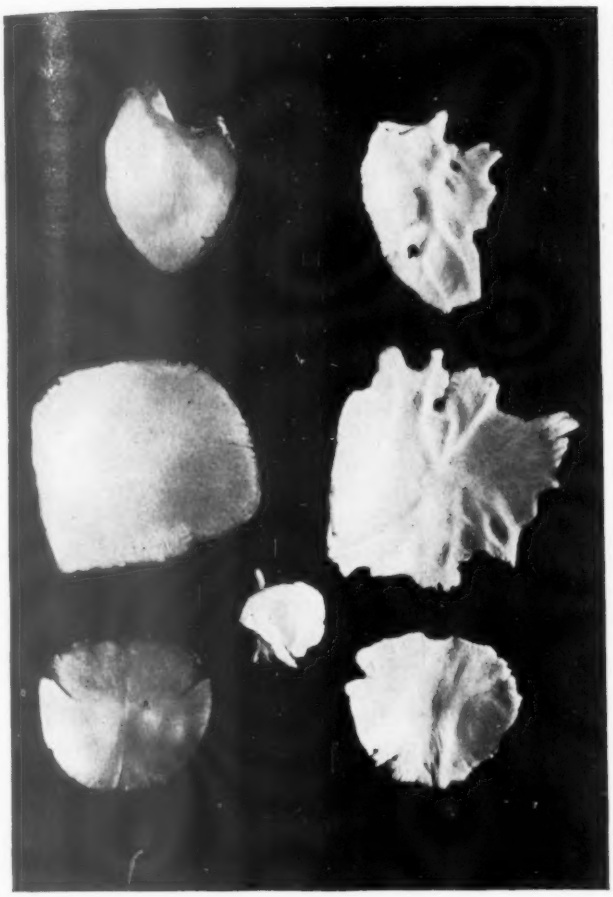

FIG. 3.—Photograph of dried vault bones showing craniolacunia alongside those of a normal foetus of the same age.

70 per cent. Further points of interest in the anatomy of these conditions are shown by the edges of the bones, which instead of being regular and finely curved, are deeply indented and tortuous (fig. 3 and 5). The bony bars themselves may be of great thickness, exceeding the thickness of the normal skull of the same age. The architecture of the bones is also distorted, for instead of a finely radiating trabeculation, from an eccentric focus in the bone to the periphery, the osseous pattern is completely promiscuous (fig. 4 and 6).

The features of craniolacunia and of craniofenestria which are of course well seen in the dried disarticulated bones themselves are equally well demonstrated radiologically, and as we have shown elsewhere, (1943b) these two conditions can be recognized from x-ray examination in utero, after birth, and in the growing child. On antenatal radiographs evidence of defective ossification of the vault is looked for, this being indicated by abnormality of outline, consisting of faults, thinning, or reduplication in otherwise normal skulls. The existence of hydramnios or hydrocephalus, although not of diagnostic significance is a warning to the radiologist to examine the outline of the vault in great detail for evidence of these defects.

When detected in antenatal radiographs, together with a spinal defect or deformity (fig. 7), or associated with evidence of craniostenosis, the findings are pathognomonic of craniolacunia or craniofenestria, although it is not always possible to distinguish between these two whilst the foetus remains in utero: much depends on the size of the mother.

At birth the defective outline of the vault will be confirmed radiologically. In craniolacunia there will be no projections beyond the margin of the vault, whilst the bars forming the coarsely reticulate pattern will be observed to be broad, and fading smoothly into the lacunar or thinned areas enclosed between them (fig. 1).

In the more striking condition of craniofenestria there may be projections visible beyond the outline of the vault. These are pathognomonic of fenestration. The pattern formed by the bars is here much greater in contrast, for the bars are thinner and of sharper outline, the transition from them to the areas of absence of ossification (fenestrae) being abrupt (fig. 2).

These appearances will be encountered irrespective of the size or shape of the infant's skull, or of hydrocephalus, extreme degrees of craniofenestria occurring in microcephalic, grossly hydrocephalic, or normal sized skulls, in all of which types one will see examples also of the mildest forms of craniolacunia.

Where it is possible to examine the dried vault bones, these findings can be confirmed and studied in greater detail. The bones may be photographed and kept for comparison with normals of the same stage of development: they may be weighed,

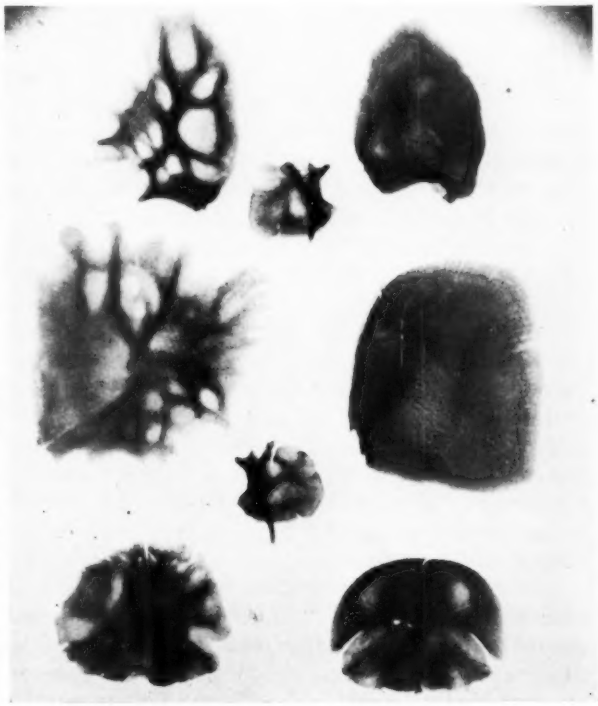

FIG. 4.—Radiograph of the same craniolacunar and normal bones revealing the poor texture, as well as the defective outlines in craniolacunia.

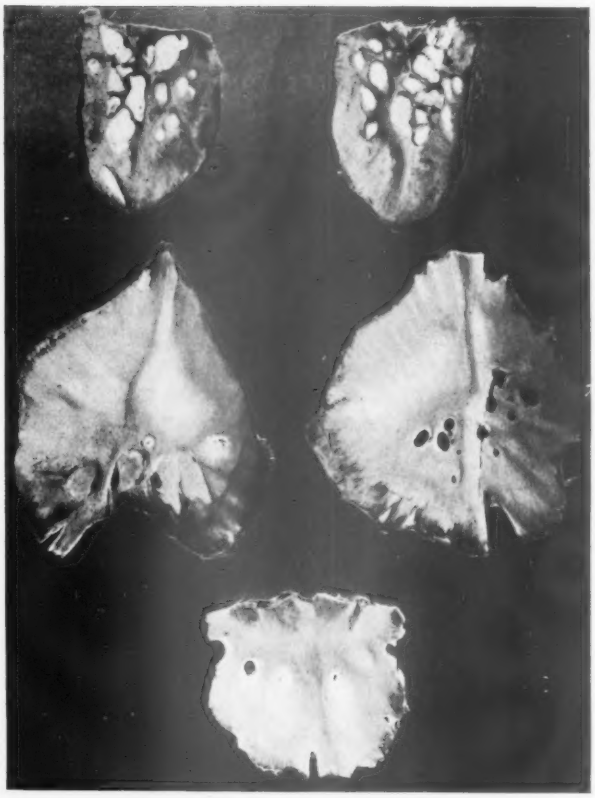

FIG. 5.—Photograph of dried hydrocephalic vault bones showing craniofenestria. The membranous covering of the fenestrae is clearly seen.

radiographed or sectioned; each process gradually building up the sum of knowledge, whilst new methods of investigation and examination are being planned.

In craniolacunia the dried vault bones when compared with normal, are found to reveal the bony bars on their inner aspects, whilst the lacunae are numerous. Isolated actual defects may be seen, but they do not form part of the pattern. It will be seen from fig. 3 and 4 that the lacunar bones are but poor imitations of the normal in three main respects, namely, ' material ', ' workmanship ' and ' finish '.

In craniofenestria the same suggestion of ' poor workmanship ' is demonstrable, but in addition there will be seen the numerous complete defects, forming a pattern against the sharply defined outlines of the intervening bony bars. In spite of the greater density of these bars in craniofenestria, the weight of each bone is grossly diminished, being sometimes as low as 22·8 per cent. of the normal (fig. 5 and 6).

In the few infants in which craniolacunia has been observed unassociated with other defects, it has gradually become less apparent and has tended to disappear with the passage of time, although it has always remained identifiable. These are the potential parents who may give birth to offspring with craniolacunia and spina bifida; if the skulls of the parents and relatives of known cases of spina bifida are x-rayed, evidence of residual craniolacunia of this type may be found.

Theories of origin

Many theories have been adduced to account for the occurrence of craniolacunia and craniofenestria, and their frequent association with spina bifida. Mechanical theories were largely suggested, chiefly by German observers, some of which were highly ingenious. Thus Kassowitz (1880) considered that external pressure on the vault bones during birth was the cause of the maldevelopment; Von Recklinghausen (1886) suggested the presence of an internal hydrocephalus which compressed the cerebral gyri against the bones with the resultant formation of lacunae and fenestrae, and bony bars which followed the pattern of the sulci. Faust (1931) thought that the cerebro-spinal fluid drained away through the spina bifida and allowed the cerebral pattern to become imprinted on the cranial bones. We have investigated all these theories and proved elsewhere that they are untenable. The analogy with ' thumbing ' of the skull produced by cases of known raised intracranial pressure we have also shown to be fallacious. To the best of our knowledge both craniolacunia and craniofenestria are purely developmental anomalies similar to spina bifida, occurring usually in association with it, but also separately.

Because the cranial maldevelopments occur so much more frequently, because they can easily be diagnosed by radiological means, and because they

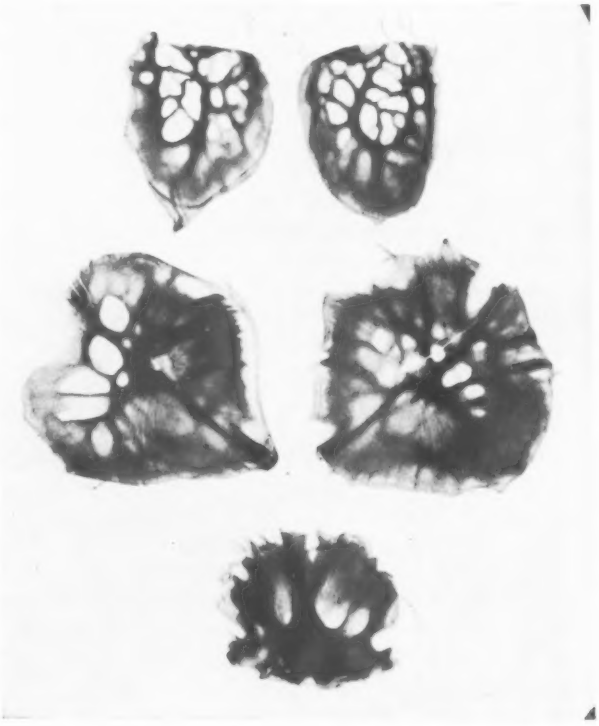

FIG. 6.—Radiographic appearances of craniofenestria. Note the increased density of the bars, and their sharp definition and relatively slight width as compared with those seen in craniolacunia.

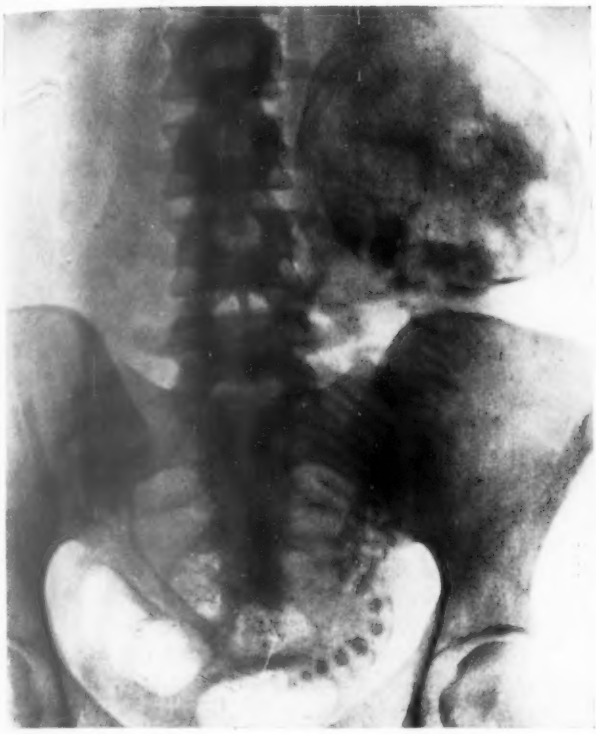

FIG. 7.—Antenatal radiograph in which the association of defective outline of the foetal vault bones with an obvious deformity of the spine enabled a confident diagnosis of craniolacunia plus spina bifida to be made before term.

are sometimes compatible with life, they offer bigger opportunities for research into their mode of production, and into the laws governing their familial transmission.

Thus in the family quoted by Butler-Smythe, it would have been of value to look for the presence of craniolacunia in the two hydrocephalic children, as well as in the three subjects of spina bifida. If the hydrocephalic reported alive at the age of two years lived to maturity and had offspring, the formation of their vault bones would be of extreme interest. Craniolacunia, moreover, offers better opportunities to study etiology, because, being diagnosable at or even before birth, it is feasible to obtain more complete data regarding the mother whilst she is in hospital, as well as to invite her collaboration during any future pregnancy. This should render it possible in the future to examine the possibility of, for example, a dietetic factor in the etiology.

The following suggestions are accordingly made:

1. That all cases of spina bifida should be x-rayed for evidence of craniolacunia or craniofenestria.
2. That skulls from all cases of twins should be examined radiologically if one or both show evidence of a congenital anomaly known to be associated with craniolacunia.
3. That skulls of parents and siblings of known cases of spina bifida should be examined in a similar manner.
4. That the offspring of known cases of craniolacunia should be closely watched for evidence of transmission of the condition.
5. Mothers of craniolacunar infants should be invited to collaborate with the obstetricians during any future pregnancy.

If in future the familial and hereditary incidence of craniolacunia is studied in this manner instead of the corresponding features of frank spina bifida, it is believed that information will accumulate with greater rapidity and will lead to the elucidation of what has always been an obscure corner of medicine.

Summary

1. The incidence rate of the developmental anomalies of the vault bones of the foetal skull known as craniolacunia and craniofenestria is shown to be nearly 1 per cent. of all births.
2. Their frequent, and little known, association with spina bifida is emphasized.
3. It is suggested that the laws governing the inheritance of spina bifida are more likely to be discovered by a study of the relatively common developmental defects, namely craniolacunia and craniofenestria (including study of the mothers of infants so affected, immediately and during any future pregnancy).

Acknowledgement

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CHILDREN IN A TUBERCULOSIS COLONY

A SURVEY OF THE PAPWORTH CHILDREN

(Based on the clinical records of Dr. L. B. Stott)

BY

E. M. BRIEGER, M.D., Papworth

The demand for statistics about the degree of infection among the Papworth children has been insistent. Sir Pendrill Varrier-Jones himself was always most anxious to supply the evidence required, but both he and Dr. L. B. Stott, who had been in charge of the children's clinic since the foundation of the settlement, were reluctant to produce any statement before a reasonable period of observation had elapsed. The present writer has been in contact with Dr. Stott since 1926, and has been privileged to follow the elaborate and painstaking method of observation which he introduced with the object of presenting one day the epidemiological picture of the village population. In 1936 Sir Pendrill Varrier-Jones decided to mark the twentieth birthday of the Papworth Village Settlement by preparing the first statistical survey, and the work has been completed and presented in a monograph which is shortly to be published. Here some results of the observations, which will be found in detail in the monograph, are submitted.

The material

Papworth Village Settlement is a community which has grown from small beginnings: from eight cottages in 1918 to 142 cottages in 1938; and the population in 1938 (twenty years after the settlement had been transferred from Bourn to Papworth) consisted of 117 ex-patients' families. During this period 199 ex-patients' families occupied cottages in the village: of these, 137 were families with children while 62 were childless. Of the 137 families, 77 are still resident, 33 have left the village following the death of the head of the family, and 27 have left Papworth for various other reasons—seven of them because the patient had completely recovered his health.

The period of residence was less than 5 years in 54 families: from 5 to 10 years in 43 families: 10 to 15 years in 26 families: and 15 to 20 years in 14 families.

In 57 families the head of the family was a persistently sputum positive case: in 63 families the head of the family had become ' sputum-converted,' and in 15 families surgical tuberculosis was present. The heads of two families suffered from a non-tuberculous but disabling lung disease.

The number of children in these 137 families were 1–2 in 61·5 per cent.; 3–4 in 25·5 per cent.; and 5–8 in 20 per cent.

Children born in the village

There were 108 children born in the village: twenty-four in families of the healthy staff, and eighty-four in families of ex-patients. Eighteen babies were born in families of sputum negative cases; sixteen in families of surgical cases; twenty-five in families of persistently sputum positive cases (in sixteen of which the father subsequently succumbed to the disease); and twenty-five in families of sputum converted cases. Although the number of cases in each division is relatively small, it is thought advisable to deal with each group separately, as the degree of exposure is naturally different in each group.

Mortality. With regard to the mortality rate we can be brief. Of the 108 children, none have died from tuberculosis. Four of them were stillborn or died a few hours after birth; one died from diphtheria at the age of two, having left the settlement; and another is stated to have died from an attack of laryngospasm after leaving the settlement. Such a low mortality is unique compared with the general child mortality in other groups of the population in town or country; and even compared with other village populations of similar size the child mortality of Papworth must be considered very low.

Case incidence of active lesions. There was no case of active tuberculosis observed among the children independent of the conditions of exposure. This includes extra-pulmonary as well as pulmonary lesions. There was, in fact, no clinical or radiological evidence of active pulmonary or non-pulmonary tuberculosis.

Case incidence of latent lesions. It was expected that in these children some evidence of a previous primary infection would be discovered, and the findings can be tabulated as follows:—

55 (or 51 per cent.) had no clinical or radiological findings.

46 (or 42·5 per cent.) had only radiological evidence of calcified foci (not exceeding those observed in a mixed child population).

5 (or 4·6 per cent.) had radiological evidence of an abortive primary lung lesion.

2 (or 1·8 per cent.) showed evidence of transient perifocal reactions.

The two cases of transient perifocal reaction were

observed in children of sputum positive patients. Of the five cases of residual primary infiltration, three were observed in children born in the families of healthy employees, one in the family of a sputum positive case, and one in the family of a surgical case.

Discussion

It is most gratifying to know that none of the children born in the families of healthy employees or of sputum-negative cases have contracted tuberculosis in an active form when living in village settlement surroundings, and particularly encouraging to find that Sir Pendrill Varrier-Jones's statement that 'no child born in Papworth of tuberculous stock has contracted tuberculosis' has been confirmed. There are reservations to be made. The number of cases in each subdivision made according to exposure is too small actually to calculate percentages; and secondly, in most cases the period of observation covers only a small part of the lifetime of an individual in which manifestations of the disease can be expected. Observations cover the first three years of life, when the acute manifestations are to be seen in children who have been exposed to intrafamiliar infection. The question then arises how our observations at Papworth compare with the results of other contact studies. This comparison is made difficult by the fact that there is no actual standard figure, and the figures given for the incidence of active cases and mortality in infants brought up in an environment of open tuberculosis vary considerably.

In 1926 Calmette calculated that the tuberculosis mortality of babies born of tuberculous mothers in their first year of life was 24 per cent. in the provinces, and 32·6 per cent. in Paris. This figure was greatly disputed, and the Paris figures were rectified in 1928 by Hazeman to be 8 per cent. for children of tuberculous mothers in the ages of one month to four years. Other investigators found much lower figures. Jorgensen and Backer (1929) in Oslo found a mortality rate of 7·1 per cent. (196 cases); 6 per cent. for tuberculosis in the first year of life. Deutsch-Lederer (1929) reported a 6·6 per cent. tuberculosis mortality rate; and Braeuning and Neumann (1929) reported 7·5 per cent. (246 cases). In a Lancashire contact study Lissant Cox (1929) found a tuberculosis mortality rate of 3·2 per cent. (from all causes 11·5 per cent.), referring to an analysis of the histories of 1486 children in Lancashire under five years of age, living in 1063 homes, in each of which were one or more adults suffering from open tuberculosis. Dow and Lloyd (1930) found a mortality rate of 1·8 per cent. in 159 contacts 0–1 year old. Turner (1930) found a mortality rate of 3·9 per cent. in 76 contacts aged 1–2 years, from families with a sputum positive fatal case. Frantz of Magdeburg (1930) found much higher figures, reporting 16·9 per cent. in 119 cases.

Ostenfeld and Kjer-Petersen (1931) found a 6·1 per cent. tuberculosis mortality rate in children exposed to infection in infancy and followed up to their third year of life. In 103 children exposed to an open case in the first and second year of life, Scherman (Munich 1931) found 12 per cent. mortality from tuberculosis.

Dieppes (1933) found that out of 688 children born between 1926 and 1930 in households in Cologne where one member suffered from open tuberculosis, 7·2 per cent. died from tuberculosis in the first year of life. The death rate from tuberculosis was 8 per cent. in 382 contact infants reported by Grass of Bremen (1934). Kandziora (1934) found a tuberculosis death rate of 9 per cent. in 65 babies born in tuberculous families.

Seiffert (1935) derived from a questionnaire sent to all the tuberculosis dispensaries in Germany that the tuberculosis mortality of contacts in the first year of life was 11·6 per cent.

Duthoit and Dubois (1936) found a tuberculosis mortality rate of 17·4 per cent. in contact infants living with a sputum positive case for one to twelve months in the first six years of life. Wirtz (1936) recorded 7·7 per cent. deaths from tuberculosis in 168 infants born in the years 1926–1933 in families where the father or mother was a sputum positive case. The mortality rate of the tuberculin positive babies was 11·7 per cent. Heynsius van den Berg (1936) in Amsterdam found the tuberculosis mortality in children exposed during the first three months of life and followed up for the first two years varying from 2·3 per cent. in good hygienic conditions and slight exposure, to 69·3 per cent. in bad hygienic conditions and massive exposure.

From these figures, collected from all over the world, it can be seen that the tuberculosis mortality of infants born in a tuberculous environment varies to a certain extent, and these variations might be explained by the conditions of exposure.

This is borne out, not only by Heynsius van den Berg's careful investigations, but Leon Bernard (1928), the French phthisiologist, also insisted upon the fact, and he used to refer in this connexion to the following observation.

In the maternity wards of a hospital for tuberculous mothers the death rate of babies dropped from 38 per cent. in 1921–1923, to 13·2 per cent. in 1923–1925, and to 7·2 per cent. in 1925–1926. This improvement was due to the fact that in the second period a separation of mother and child was secured by keeping them in different rooms, but in contact with their mothers; while in the last period the babies were removed from the building altogether.

Whatever the interpretation might be, the fact remains that the expected tuberculosis mortality of children born in families with an open case varies over a wide range. Most of the figures lie between 2 per cent. and 10 per cent.

It is important to note that the babies born in Papworth do not form a 'collective': they are not an aggregate of cases exposed under identical conditions. The exposure varies in the different families, and the number of babies born in the homes of open cases is too small for comparison of statistical calculations. But still there remains the fact that in the scale of investigations Papworth takes the lowest place. This cannot be merely accidental, as at the same time there is a complete absence of other manifestations of activity, such as primary in-

filtrations or glandular enlargements. The incidence of active cases of tuberculosis is much higher than the mortality, though reliable figures about morbidity are not easily obtainable.

One question cannot be answered satisfactorily, that of the infection rate. Dr. Stott had subjected the children to the Moro test as a routine method, and his results were reported by Bardswell in 1933 at the Annual Conference of the Tuberculosis Association at Cardiff. Stott found 63 per cent. positive reactors in the second year of life, or 56·8 per cent. in the age group one to five (referring to 91 cases aged one to five). This figure is on the low side compared with other statistics. Heynsius van den Berg assessed the infection rate at 71·5 per cent. in contact infants in the first year. The infection rate in children exposed in the first year of life and observed during the first two years, varied from 31·2 per cent. in good hygienic conditions and slight exposure, to 100 per cent. in bad hygienic conditions and massive exposure. Seiffert, in his mass survey, found 71·6 per cent. to 79·3 per cent. positive reactors in child contacts under five years old, and the figures of other investigators are on a similar scale.

It might, therefore, be said that the infection rate and the extent of the infection among the babies born in Papworth corresponds to that observed in tuberculous families where almost ideal home conditions prevail.

Children admitted to the village

After this discussion of the children born in Papworth, there remains the bulk of the childhood population which has been admitted to the village with their families at various ages, and who were exposed to intrafamiliar contact infection before admission. These are families which have been transferred from their former environment to Papworth after the damage has been done, and there are, therefore, two aspects to be discussed: (a) the spread of infection among these families as a result of exposure before admission, and (b) the effects of the new surroundings upon the development of primary infection.

The standard method for examining the spread of infection in families where one of the parents is the source of infection is the family chart. There are several ways of working out such a chart which was first applied by the late Sir Arthur Newsholme. A very well-known example is the chart worked out in Opie's contact studies at the Phipps' Institute at Philadelphia. The principle of all these charts is the chronological follow-up of all the members of the family in relation to their exposure, and the recording of all the clinical and radiological observations made during the actual period of exposure, and the subsequent follow-up of each individual member.

The type of family chart used in the Papworth survey can be seen from a few examples reproduced when discussing the extent of family epidemics that victimized a number of families before admission to the settlement. Each member of the family is designated by a capital letter (A=father; B=mother; C=first child, and so on). The years are marked horizontally, and each member of the family appears vertically. Negative sputum is indicated by two parallel lines: active disease with positive sputum is indicated by blacking out the space between these lines. If no sputum records are in existence, the upper line is broken; if there is active surgical disease, both lines are broken. The circles on the lines of the dependents indicate the dates when x-ray films were taken, and the number inside the circle, together with the shading refers to the system of case-type definitions which are explained at length in the monograph. Each x-ray film has been reproduced on to a small Leica strip, and from these strips copies have been made on the diagrams. The x-ray films are identified as follows: 1A 28=the first x-ray taken of the father in 1928; 2A 30=the second x-ray of the father taken in 1930, and so on. The time of entrance to the village is indicated by the vertical line.

Family charts were made for 239 families who resided in the village, including the families of the healthy staff.

Family epidemics. In a number of families there was a family epidemic in evidence before admission to the village. Family charts 37, 42, 64 and 122 are extreme examples (fig. 1–4). Conjugal infection had occurred in thirteen families. There were ten cases of open tuberculosis, and four cases of closed pulmonary tuberculosis observed in the wives of patients, suggestive of conjugal infection. This would amount roughly to 14 per cent. total, or 10 per cent. open cases among conjugal contacts, if we consider only conjugal contacts who were exposed to an open case.

This indicates a rather higher rate of conjugal infection compared with the average figures reported in the literature. These figures vary considerably. Arnould (1933) in a mass survey on 5369 cases reported 8·4 per cent.; Opie (1932) in a survey on 535 cases reported 12·5 per cent. The figures observed in Papworth, taken in conjunction with the impressive evidence of family epidemics in admitted families, are an indication that the families which applied for and received admission to Papworth were representative of the average contact population.

This is further shown by the mortality and incidence of active and latent lesions in the children of these families. There are 151 children in this group: 76 were under five years old on admission; 67 were of school-age (6–14); and eight were over fourteen years of age. The highest incidence of active childhood lesions was observed in 112 children below the age of ten years: three cases of active childhood tuberculosis and 31 cases of x-ray findings suggestive of residual primary infiltration. Among the 39 children over ten years of age, there was only one case of active childhood tuberculosis: two cases of residual primary infiltration; but nine cases of adult phthisis.

These are indeed record figures. None of the active childhood type of lesions developed during the stay at Papworth ; the adult type lesions were in nine cases present on admission, and four other cases

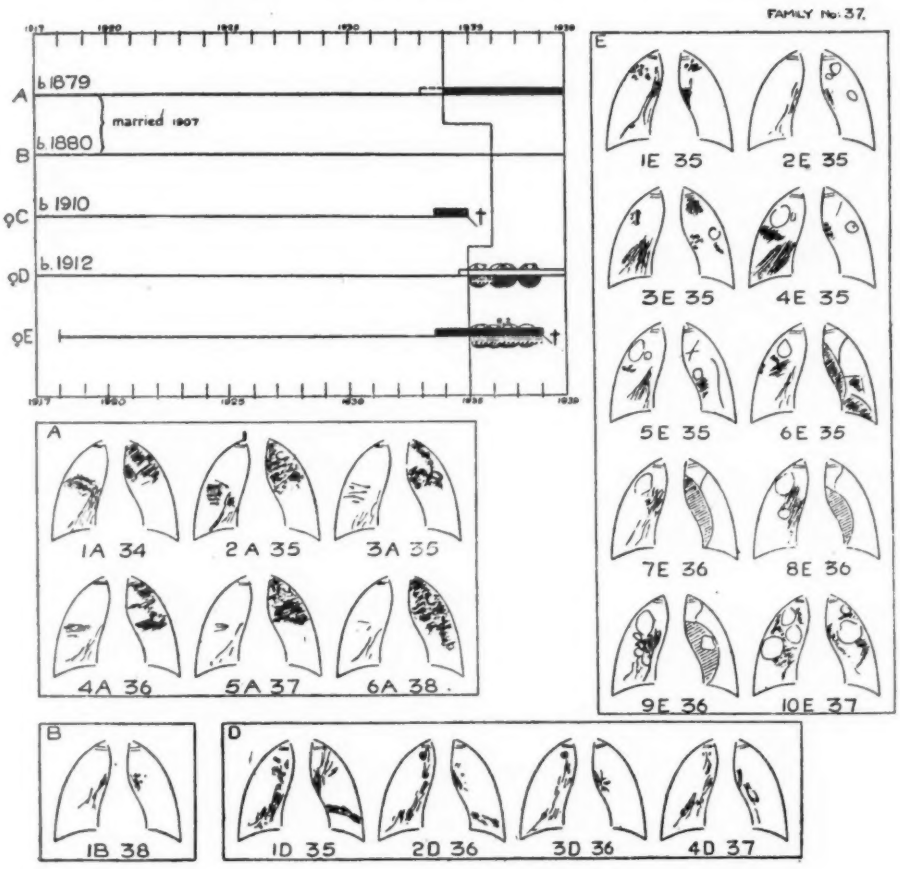
FAMILY No. 37.
A
b 1879
married 1907
B
b 1880
♀C
b 1910
†
♀D
b. 1912
♀E
†
1917
1920
1925
1930
1935
1939
A
1A 34
2A 35
3A 35
4A 36
5A 37
6A 38
B
1B 38
D
1D 35
2D 36
3D 36
4D 37
E
1E 35
2E 35
3E 35
4E 35
5E 35
6E 35
7E 36
8E 36
9E 36
10E 37

FIG. 1.

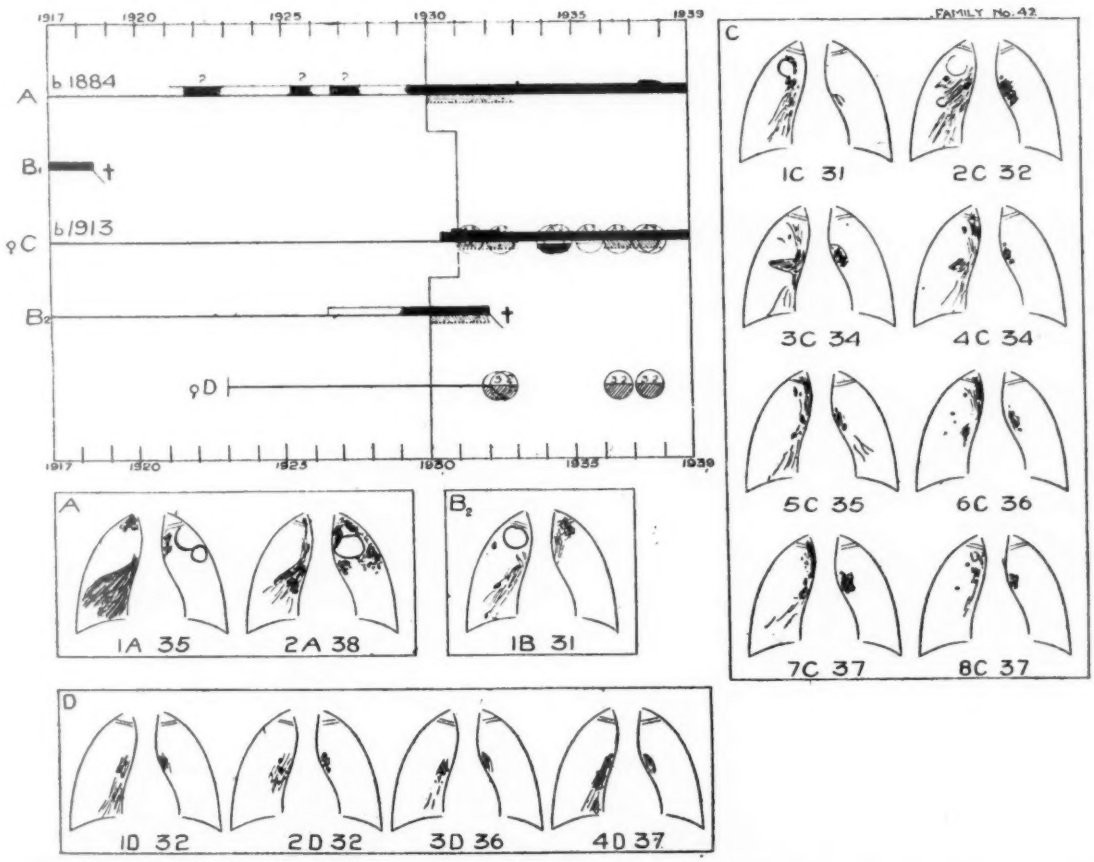
FAMILY No. 43
1917
1920
1925
1930
1935
1939
A
b 1884
?
?
?
B1
†
♀C
b 1913
B2
†
♀D
C
1C 31
2C 32
3C 34
4C 34
5C 35
6C 36
7C 37
8C 37
A
1A 35
2A 38
B2
1B 31
D
1D 32
2D 32
3D 36
4D 37

FIG. 2.

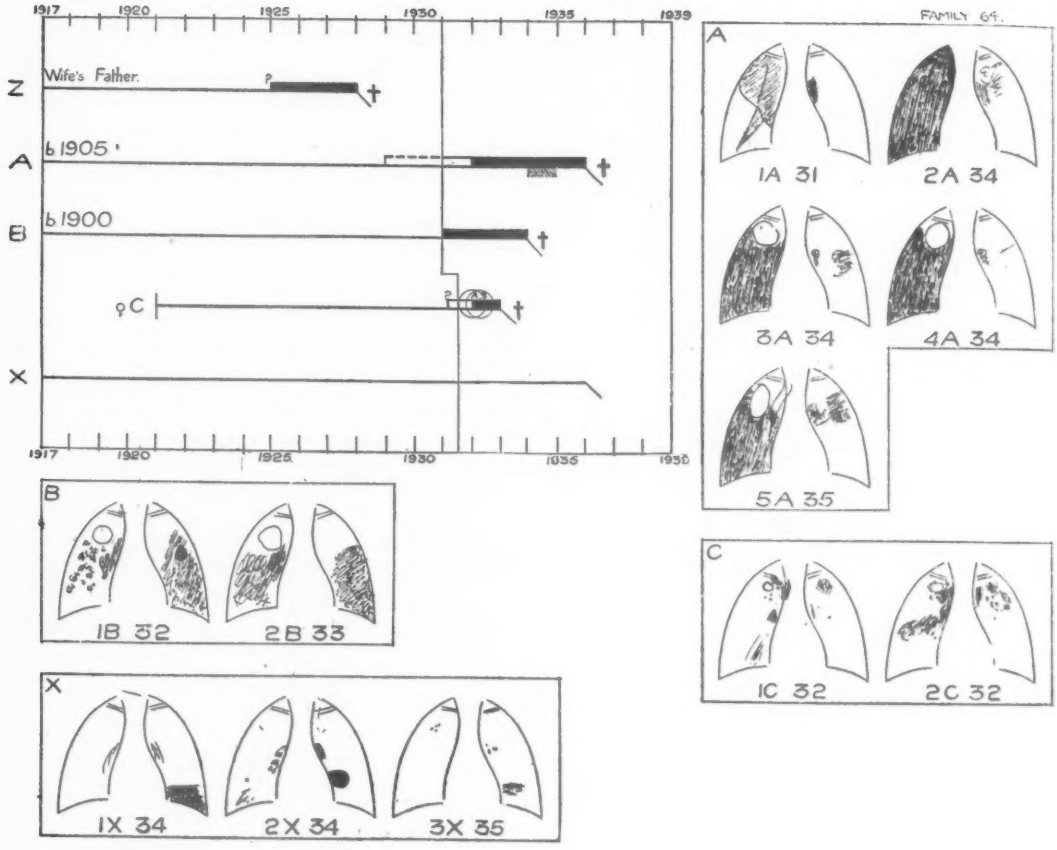
1917
1920
1925
1930
1935
1939
Z
Wife's Father.
A
b. 1905
B
b. 1900
♀C
X
FAMILY 64.
A
1A 31
2A 34
3A 34
4A 34
5A 35
B
1B 32
2B 33
C
1C 32
2C 32
X
1X 34
2X 34
3X 35

FIG. 3.

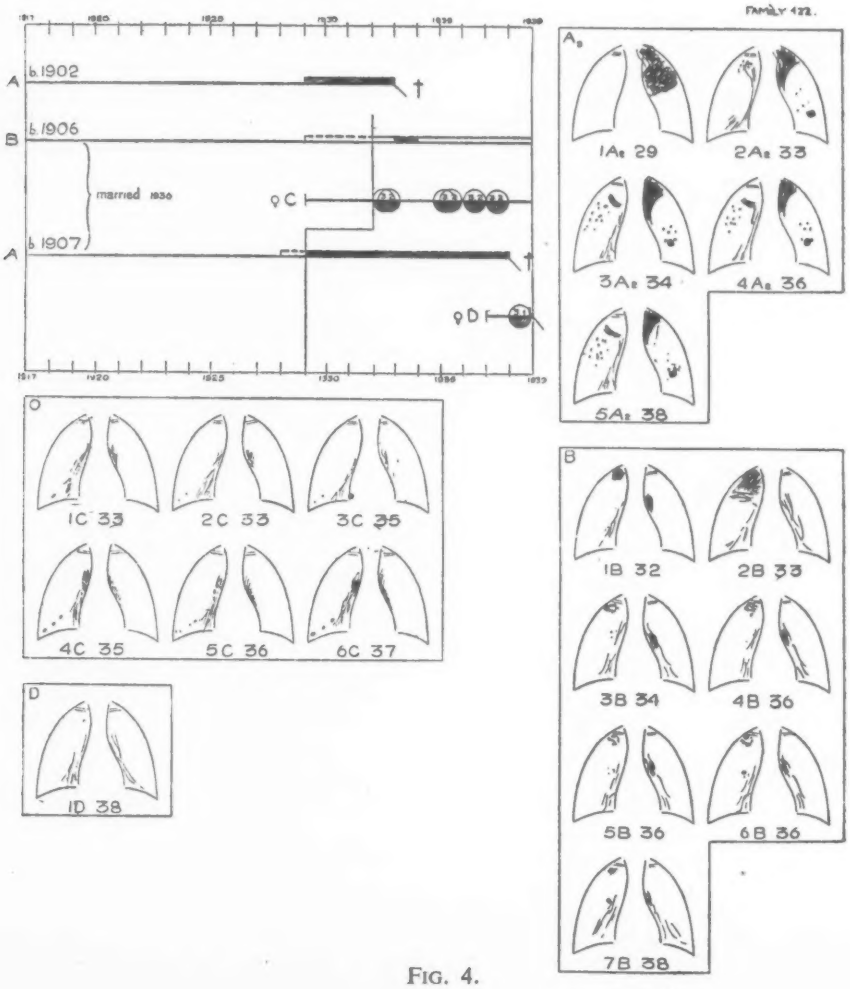
A
b. 1902
B
b. 1906
married 1936
♀C
A
b. 1907
♀D
FAMILY 172.
A
1A 29
2A 33
3A 34
4A 36
5A 38
B
1B 32
2B 33
3B 34
4B 36
5B 36
6B 36
7B 38
C
1C 33
2C 33
3C 35
4C 35
5C 36
6C 37
D
1D 38

FIG. 4.

developed recently while under observation in Papworth.

In order to give a more accurate picture of the course of contact infection in these children the example of Opie and McPhedran has been followed, and the children grouped according to their age on exposure, and each group followed up separately, the interval between exposure and the first clinical signs of active lesions being recorded.

Among the 116 children who were 0–4 years at the beginning of contact:

28 had no clinical or radiological evidence of lesions;
7 had Ghon foci;
47 showed the usual type of calcification;
26 had some radiological evidence of a residual primary infiltration;
2 showed perifocal reactions;
4 had active childhood lesions;
2 showed symptoms of early adult phthisis.

The incidence of latent childhood lesions characteristic of a preceding primary infection is 20·6 per cent.; of active childhood tuberculosis 3·4 per cent.; and of early adult lesions 1·8 per cent. Those free from clinical or radiological symptoms are 24 per cent.

The next group of children, whose ages were 5–9 years at the beginning of contact, is comparatively small, and includes only twenty-three children. There is, of course, no statistical calculation possible about the incidence of lesions, but it is evident that in this group the picture so characteristic of a preceding primary infiltration is practically absent. There is one case of perifocal reaction; no case of childhood tuberculosis, but there are four cases out of 23, or 17·4 per cent., which show signs of more or less progressive adult phthisis.

The next group with the contact age of 10–14 years is too small from which to draw any conclusions, and the same applies to the group 15–25 years old at the time of exposure. It must be noted, however, that the three cases known as adult contacts were also suffering from adult phthisis.

Discussion

It is not in any way surprising that the infection rate and case incidence in the children exposed before admission to Papworth shows the alarming picture so familiar to the student of contact epidemiology. The figure for active lesions is deceptive, as no cases were recorded here who had died before the family came to Papworth or who did not come with the family for any reason. It is not of so much interest to know how many children had active tuberculosis when they arrived at Papworth as how many developed lesions in later years while under observation in the settlement. In other words, was the rate of exacerbation that to be expected in contact children, or was there any variation from the expected figures?

It is now generally recognized that contact infection in childhood often leads to the reaction which is known from the description of Kuss and Ghon as primary, or initial childhood tuberculosis. The majority of the contact children showed manifestations of such primary infection. The great majority had only latent lesions, but nevertheless might develop the adult type of phthisis after an interval of varying length. If contact infection takes place in later childhood, or in young adult life, the signs of primary infection are usually less obvious; while the development of adult type phthisis follows after a much shorter interval. The importance of this time interval has been shown by Jessel (1930), Macpherson (1936), and especially by Opie and McPhedran (1932) in their extensive contact studies on family contacts. It is there shown that in contacts exposed between 0–9 years of age the mean frequency of tuberculous lesions indicative of a clinically manifest tuberculosis is 3·95 per cent. in the three years following exposure; and 13·45 per cent. in cases 10–14 years after. Thus infection in childhood produces a rise in the incidence of active childhood lesions in the years following exposure; then comes an interval when active lesions are rare; and this is followed by a peak in the incidence of adult type lesions. If the infection takes place in young adult life (fifteen or higher) there is a rising incidence of active lesions from 2·69 per cent. in the year following exposure to 10·59 per cent. 4–5 years after exposure, and to 19·05 per cent. 10–15 years after exposure.

If this picture is accepted as showing the trend of the development of contact infection in childhood contacts, it is reasonable to expect in the children admitted to Papworth the appearance of adult type lesions. In fact, such exacerbations were observed in only two cases in 0–4 years contacts, both quite recently, and one exacerbating while serving with the Forces. Although 30 of the 116 children who were 0–4 years at the beginning of contact have now reached puberty, only two cases of adult phthisis were discovered in addition to the two which were present on admission. This figure is definitely below the expected one, but it is not inferred that residence in the village settlement has been responsible for this satisfactory result. In the two other cases where active and fatal pulmonary tuberculosis developed in recent years, one was a four to nine years' contact, the sister of one of the cases mentioned before. The other was a case of congenital heart disease who suddenly developed fatal adult type phthisis.

It can thus be seen that the picture observed in Papworth fits in quite well with the general picture obtained from other contact studies, with the one difference that since the families took up residence in Papworth the rate of adult type exacerbations was not alarming, and might have been even less if war conditions had not had their repercussions in one way or another on the village life. The point must be stressed that out of the four cases of late exacerbation only one (the case of congenital heart disease) actually occurred in the village, the other three being recorded in one case during military

service, and in the other two cases after the families had left the village. A full description of all the case types observed is given in the monograph.

Case types

It is important not to be too dogmatic about the interpretation of the different stages of contact infection. From the clinical point of view three phases in the development of contact infection must be distinguished: the phase of initial infection, the interval, and the phase of phthisical development. In a great many contact cases all three phases are discernible. There is the initial lung lesion following exposure, a typical picture in children, but also seen in adults; there are interval symptoms of a more or less definite nature; and finally there are the signs of the development of phthisis. In other cases there is no visible initial reaction, and in others again there may be no interval symptoms.

Several theories have been put forward to account for the protracted character of contact infection. There is no doubt that in a great many cases phthisis in adult contacts develops in an apparently healthy lung without any other preliminary signs of symptoms, except the fact of exposure. These cases have always been a problem. It has been shown that in such cases x-ray films have appeared normal up to three to six months before the actual onset of adult phthisis.

There are cases, however, in which continuity of development can be followed on the x-ray film, and in the two following examples the development from the initial lesion to the final phase of adult phthisis could be watched.

Family 70. In this family the father and daughter were both suffering from pulmonary tuberculosis. The son was still a child when his father developed the disease, and was of school age when his sister was discovered to be an open case. An x-ray film taken at the age of eight years showed some calcified foci in the left hilum. When he was fourteen years old an oblong calcified lesion was present in the left middle zone, also a group of calcified foci in the right hilum. These were definite indications of an active initial lesion. The x-ray findings were closely followed up, and two years later a soft, partly calcified focus, 1 inch wide, was recorded in the left apex with visible streaks leading to the hilum. There was no sign of any further developments, and he was accepted by the Army at the age of twenty. Two years later he broke down, and was readmitted to Papworth. A cavity was present in the left upper lobe on the site of the apical focus seen in the previous x-ray films.

Family 96. In this family the father developed open tuberculosis and finally succumbed. One daughter, thirteen years of age on admission, was suspected of having an active initial lung lesion. Calcification developed in the course of time, and when she was twenty years old a number of hard foci were seen in the left apical region. In the following years a definite spread developed in this zone, and the case was classed as a case suspect of pre-phthisical symptoms. The family left the village and the girl married and had a child. She was readmitted to Papworth in 1940 with a large cavity in the left upper lobe at the site of the former lesion. She finally died in hospital. One brother developed acute tuberculosis at about the same time; his case falls into another category and will be discussed elsewhere.

It is most probable that this type of evolution is the rule, although not always demonstrable in the clinical or x-ray findings. Anatomical investigations at Papworth confirm the view lately taken by Sweany, that the contact lesion which develops after exposure might produce by its insidious but continuous growth all the symptoms that we observe during the interval. There is apparently no essential but only a gradual difference between the development of a contact lesion in children and adults.

Conclusions

The following table shows the incidence of lesions in the various groups of children admitted to the village, compared with that in the village-born children up to 1938.

It will be seen that the village-born children and the children of the healthy staff show the same low incidence; while the children in families of sputum negative and surgical cases show perhaps a slightly increased incidence. In contrast to this the children

TABLE COMPARING THE INCIDENCE OF LESIONS IN THE VARIOUS GROUPS OF ADMITTED CHILDREN AND IN THE GROUP OF CHILDREN BORN IN THE VILLAGE (ALL FAMILIES INCLUDED)

Type of lesion	CHILDREN ADMITTED IN FAMILIES OF			Village-born children (all families)
	Healthy staff	Sputum neg. and surgical cases	Sputum pos. cases	
No clin. or rad. evidence ..	13 (40·9 per cent.)	25 (32·5 per cent.)	37 (24·5 per cent.)	55 (51 per cent.)
Ghon foci	2 (6·1 per cent.)	6 (7·8 per cent.)	9 (5·9 per cent.)	6 (5·5 per cent.)
Calcified foci	16 (50 per cent.)	43 (55·8 per cent.)	64 (42·4 per cent.)	40 (37 per cent.)
Residuum of primary infection	0	2 (2·6 per cent.)	25 (16·6 per cent.)	5 (4·6 per cent.)
Transient perifocal reaction ..	1 (3 per cent.)	0	3 (2 per cent.)	2 (1·8 per cent.)
Childhood tuberculosis ..	0	1 (1·3 per cent.)	4 (2·7 per cent.)	0
Adult phthisis	0	0	9 (5·9 per cent.)	0
TOTAL	32	77	151	108

of sputum positive cases show, as would be expected, a high degree of infection, indicating that contact infection has produced a kind of contact epidemic with a great variety of lesions, before they came to Papworth.

With regard to prognosis, more time must elapse. It has been shown that in contacts the exacerbation rate in later age groups depends on the activity of infection in childhood. In a contact population, if the active childhood lesions are very numerous high figures for adult phthisis have to be expected. If, as in the case of the village-born children, the number of active initial lesions are extremely few, a rise in adult exacerbations need not be feared so long as the resistance of the individual and the environment are under control. For the same reason the children admitted to the village must be carefully watched for possible exacerbations, although there is reasonable hope that their present environment, by building up resistance, might have the effect of preventing, in a great number of cases, later exacerbations.

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CASE REPORTS

INTESTINAL THRUSH

A REPORT OF TWO CASES IN YOUNG INFANTS

BY

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The rarity of intestinal thrush, occurring either as a complication of oro-pharyngeal or oesophageal thrush, or as a primary infection, warrants the publication of two cases recently observed by us. The affected infants were both under two months old at death. Both were prematurely born, one at home and admitted to hospital in a moribund condition, and the other very prematurely born and nursed in a maternity hospital.

Infection of the mouth with the fungus Monilia albicans is common in young infants. The incidence of oral thrush is particularly high in nurseries and in artificially-fed infants owing to the ease with which the infection is spread in these circumstances. It is unfortunate that oral thrush is usually regarded as a benign condition unworthy of thorough treatment, for the risk that the infection may spread down the oesophagus and beyond is always present. Routine post-mortem examinations in maternity and children's hospitals have shown that thrush oesophagitis is not an uncommon complication of oral or pharyngeal thrush. The infection spreads to the gastric mucosa in only a small proportion of cases of thrush oesophagitis, however, and involvement of the intestinal mucosa is rare. Ludlam and Henderson (1942) reported twenty cases of thrush oesophagitis in a maternity hospital during a four-year period. This serious complication of oral thrush, demonstrated post-mortem by one of us (A.R.M.), was regarded as the cause of death in thirteen instances. The second of the two cases of intestinal thrush recorded here was mentioned by these authors in the pathology section of their paper. Ebbs (1938) recorded a series of twenty-eight cases of acute oesophagitis in infants under ten months old who were observed in a children's hospital over a period of three years. The condition was caused by the thrush fungus in twenty-two of these cases. None of them showed any gastric involvement, but small pin-point ulcers were found in the colon in two.

The mycelial strands of the thrush fungus may penetrate deeply into the mucosa of the oesophagus, stomach or bowel, readily invading lymphatics and veins (vide Ludlam and Henderson), and lesions in distant parts of the body may follow infection of the blood-stream. The organisms would appear to be destroyed in the blood as a rule, for pyaemic lesions are rare. Nevertheless, lesions have been reported in the following tissues: brain, lungs, kidneys, joints, bones. Infection of the following surface tissues in infants has also been recorded: trachea and bronchi, vagina, prepuce, conjunctiva, middle ear and mastoid cells, skin.

Case reports

Case 1. Margaret McG., born January 20, 1942, died February 16, 1942, aged one month.

HISTORY. A firstborn illegitimate child who was born at home of a twenty-year-old mother. The birth weight was about 5 lb. The infant was breast-fed for three days only, ' owing to difficulty with fixing and sleepiness.' It was then given cow's milk and water in equal parts by spoon. Progress was said to have been satisfactory up to the age of three weeks. The appetite then deteriorated and the mouth ' bled when touched.' Two or three days later, the mother noticed a white coating on the mucosa of the mouth and the baby had become grey and ' pinched looking '; there had been six or seven loose, green stools per day for a week. At this stage of the illness the baby was admitted to the Royal Edinburgh Hospital for Sick Children, aged twenty-seven days.

On admission to hospital, the baby was in a weak, emaciated and dehydrated condition and weighed only 3 lb. 12 oz. The dorsal surface of the tongue and the mucosa of the cheeks and palate showed numerous patches of thrush. Some of these lesions were bleeding. The abdomen was not distended, but felt somewhat doughy on palpation. Death occurred seven hours after admission to hospital.

Necropsy. The body was that of a small, poorly nourished female infant. The umbilicus was healed.

ALIMENTARY TRACT. The mouth showed numerous thrush deposits on the cheeks and palate. The tongue did not show any thrush. The pharynx and oesophagus showed inflammatory reddening of the mucous membrane and slightly adherent deposits of thrush, under which superficial ulceration had occurred. These were present throughout the whole length of the oesophagus. The stomach was healthy. The small intestine, for about two feet in the middle, showed considerable swelling and congestion of the wall with diffuse superficial ulceration of the mucous membrane. Much faecal matter adhered to the ulcerated surface and among this were small yellowish masses resembling thrush colonies (fig. 1). These were slightly adherent but could be removed without much difficulty. The appearance was not unlike that of an acute dysentery except for the unusual situation. There was a little congestion of

FIG. 1.—Small intestine showing masses of lightly coloured, adherent thrush colonies.

the mucous membrane of the ileum, close to the ileo-caecal valve, but this part showed no swelling or ulceration. Other parts appeared to be quite healthy. The colon was healthy.

Head, respiratory passages, lungs and heart: nothing of interest was found.

Liver, spleen and kidneys: these organs were dark, firm and atrophic.

BACTERIOLOGY. Films from the oesophagus and the ulcerated part of the small intestine both showed the presence of thrush organisms in large quantities. A culture of the faeces on MacConkey's medium did not show any pathogenic organisms. No culture was made on Sabouraud's medium.

HISTOLOGY. The small intestine showed extensive ulceration of the surface of the mucous membrane. A slough of necrotic material intermixed with bacteria covered the surface. Under this, the submucosa was infiltrated with inflammatory cells and greatly congested. This encroached on the inner part of the muscularis but did not penetrate further through the wall. The bacteria in the slough were mostly Gram positive cocci and rods. Spores and mycelium of the thrush organism were present also but not in large amount, and they had not penetrated the substance of the intestinal wall.

Case 2. Elizabeth Ann B., born March 13, 1941, died May 6, 1941, aged seven and a half weeks.

HISTORY. A much premature infant of thirty-one weeks' gestation. The birth weight was 3 lb. The infant was fed on breast milk and made excellent progress. She weighed 4 lb. 9 oz. at the age of six and a half weeks. Fretfulness then appeared, although the appetite remained good and the stools normal. The abdomen became distended on the second day of the illness and there seemed to be abdominal pain. Measures were taken to relieve the meteorism and sulphathiazole therapy was started. Some improvement occurred after two days and this continued for three days, after which the infant's condition seemed to be fairly satisfactory. This was followed by the reappearance of restlessness and a deterioration in the general condition. The infant collapsed the next morning and died an hour later. No thrush lesions were seen in the mouth either before or during the illness, but small oral lesions or pharyngeal lesions might easily have been missed. There was never any vomiting and the stools were said to have been normal throughout the illness.

Necropsy. The body was that of a small but not very poorly nourished female infant. The umbilicus was healthily healed.

ALIMENTARY TRACT. The mouth and tongue did not show any evidence of thrush, nor did the pharynx or oesophagus. The stomach was healthy. The small intestine showed a solitary ulcer about six inches above the ileo-caecal valve. It was about half a cm. in diameter, circular and shallow, with a slough adhering to its base. Otherwise, the whole of the small intestine was perfectly normal in appearance. The colon was healthy.

The head and respiratory passages were normal.

The lungs showed congestion and oedema of the bases.

Heart: there was a little dilatation.

Peritoneal sac: nothing abnormal was found.

Liver, spleen and kidneys: these organs showed nothing of interest.

BACTERIOLOGY. A culture on MacConkey's medium of the faeces from the site of the ulcer did not reveal any organisms of the dysentery or enteric groups. No culture was made on Sabouraud's medium.

HISTOLOGY. The ulcer in the ileum was found to be a thrush lesion. The slough on the surface was composed of the mucous coat of the bowel, thickly infiltrated with inflammatory cells and with spores and mycelium of Monilia albicans. The ulcer penetrated to the outer muscular layer, the floor showed inflammatory infiltration and invasion by strands of mycelium. The mycelium could be detected passing through the wall almost to the subserous coat and a fragment of it could be seen in a subserous lymph vessel. A feature of the section was the presence of many eosinophil leucocytes in the edges and floor of the ulcer.

Comment

There can be little doubt that, in both cases, thrush was the cause of the intestinal lesions. In the first case, there was an obvious source of infection in the mouth, pharynx and oesophagus. The thrush organisms had not penetrated deeply into the intestinal wall, but they were plentiful in films made from the ulcerated surface. No other pathogenic organisms were discovered, and the site of the ulceration was unusual for any form of dysentery or enteric infection. The intestinal lesions were probably not of long duration, their superficial character being thus accounted for.

In the second case, the histological features of the ulcer near the lower end of the ileum were quite characteristic of thrush, and mycelium was demonstrated penetrating deeply into the floor. This case is of particular interest, as the ileal ulcer was the only evidence of thrush of the alimentary tract. The possibility that it was a secondary lesion cannot be excluded, however, for slight oral infection often remains undetected.

Thanks are due to Dr. Margaret Martin, paediatrician to the Elsie Inglis Maternity Hospital, for permission to publish the second case.

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TRANSECTION OF THE SPINAL CORD DUE TO INJURY AT BIRTH

BY

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'In breech deliveries traction on the lower extremities may cause injury of the spinal cord amounting sometimes to physiological transection, even in the absence of actual fracture of the vertebrae.'

This quotation from Holt's Diseases of Infancy and Childhood (1936) has been dramatized in the following case, which is deemed worthy of report on account of the apparent rarity of the condition, the absence of recent reports in British and American literature since those of Crothers and Putnam (1927), and the extreme rarity of a description of certain of the histological changes.

Case report

J.S., a girl aged nine months, was admitted to the Adelaide Children's Hospital in December, 1940, and died at the end of a fortnight.

The obstetrical history was as follows: the mother, a young primipara, at full term required turning of the foetus from a vertex to a breech presentation for treatment of placenta praevia, and delivery was completed under general anaesthesia. The infant weighed eight pounds five ounces, and no unusual difficulty was experienced in delivery. The obstetrician did not consider that undue traction had been required. The baby had appeared quite well immediately after birth, but a gradually increasing paralysis of the legs was noticed two weeks later, and catheterization had to be carried out for retention of urine.

The mother stated that the baby was an active child and moved her head and arms freely, but all her life had never moved her legs very much. She was not able to sit up, and at times was unable to empty her bladder properly.

On examination the child was found to have a normal facial appearance and appeared mentally normal. She moved her head and arms freely and naturally. The upper part of the chest was flattened equally on both sides, the lower ribs were splayed outwards. The upper portion of the chest down to the level of the third ribs moved normally with respiration, but below this level, with each inspiration the chest was drawn inwards and the abdomen bulged. There was a bilateral flaccid paralysis of the abdominal muscles, and the superficial abdominal reflexes were absent. The legs lay motionless and flaccid, and the tendon reflexes were not obtained. Stimulation of the soles of the feet produced a mass reflex. It was not possible to assess sensation over the trunk and limbs. Bed-sores had not developed, and there were no abnormal areas of sweating. From these signs a diagnosis of a transverse myelitis was made although its cause was still obscure.

A skiagram of the spinal column was then taken and did not show any abnormality. Lumbar puncture was next carried out, but the pressure would not register, and only one cubic centimetre of slightly bloodstained fluid could be obtained. Pressure on the veins of the neck did not produce any increase of fluid. There were 192,000 red cells and 300 white cells per c.mm. and the supernatant fluid was a definite yellow colour. These findings suggested a Froin's syndrome and iodized oil injected into the theca in the lumbar region showed a complete block at the level of the body of the fourth dorsal vertebra; a similar injection by puncture of the cisterna magna showed that the upper limit of the block was at the level of the second dorsal vertebra.

The child died of pneumonia and permission was given to examine the spinal cord only. From the level of the second to the fourth dorsal vertebrae in the spinal canal the dura mater could not be separated from the spinal cord; dense adhesions in this area obliterated the normal space between the cord and the dura mater. Above and below this area, which was about one inch long, the normal space was present and the cord appeared normal to the naked eye. There was not any deformity of the spinal column. There was no cystic degeneration of the meninges in the area in question, nor was there any discoloration suggesting altered blood clot.

A section of the spinal cord taken through the level of the adherent meninges showed a mass of fibrous tissue of some considerable standing, judging by the maturity of the fibrous tissue cells. In the centre of this tissue the central canal of the spinal cord could be identified and scattered elsewhere throughout it were isolated areas of nerve fibre tracts seen in transverse section. There was a certain amount of fat present, mostly at the periphery, and a considerable growth of small vessels extended from the pia into the periphery of the cord. The whole was infiltrated by a number of mononuclear cells, some of which resembled plasma cells. In the whole of this section there was nothing resembling a nerve cell.

A section taken at the lower end of the area in question passed through recognizable spinal cord, but in one posterior horn there were several areas of softening, and judging by one anterior horn, a

considerable loss of nerve cells in the opposite horn. There was no evidence of a pyramidal tract. There was a considerable proliferation of arachnoid cells with thickening of the pia mater so that the normal arachnoidal cavity was practically obliterated.

Below the level of the lesion the sites of the direct and crossed pyramidal tracts contained no myelin sheaths.

No pigmentation was seen in any section.

Discussion

The unusual finding of complete transection of the spinal cord in an infant was shown in histological section to be traumatic in origin. It was not, however, of the type that follows a haematomyelia as there was no pigmentation, the changes were not cystic nor glial in type and they were not limited to the cord itself. It was not a typical adhesive arachnoiditis as in this condition fibrosis is limited to the meninges and the cord suffers only secondarily the changes of compression. The fact that fibrous tissue was found in the normal position of nervous tissue implies a preliminary breach of the pia mater in this region.

Direct violence as the cause of such changes would necessitate gross local trauma of the vertebrae or the penetration of a foreign body between them. As there was no wound nor deformity in the dorsal region and a skiagram of the spinal column was normal such a cause is discounted.

In adults the upper dorsal region is a most unusual site for injury due to indirect violence, but in injuries at birth, Crothers (quoted by Ford, 1937), in a study of similar cases, states that the lesion occurs almost always in the lower cervical or thoracic segments. He points out that birth injuries of the spinal cord are unlike spinal injuries of any other type in that they are usually due to stretching of the cord and not to compression. The spinal cord is delicate and inelastic, and is relatively fixed by the medulla and brachial plexus above and the cauda equina below. On the other hand the spinal column of infants may be stretched very easily as the ligaments are elastic and the muscles weak. Strong traction in the long axis of the body may therefore be expected to rupture the spinal cord before stretching the spinal column to its limits.

That the injury occurred at birth and not later is supported by the history of an unusual breech delivery in which traction must have been exerted, though it apparently was not severe. It is significant that some disturbance of the lower limbs and bladder was noticed about two weeks after birth.

If such profound injuries can be produced by manipulations that are not considered excessive it is reasonable to suppose that minor injuries are often produced during difficult breech deliveries and are overlooked. It is possible that obscure muscular or skeletal affections of the lower limbs in childhood may be related to birth trauma of this type.

Summary

A case is described of complete transection of the spinal cord in an infant.

Reasons are given for considering that the condition was traumatic in origin and was produced by traction on the body of the child during an unusual breech delivery.

It is suggested that otherwise obscure diseases of the lower limbs may be related to birth injuries of the spinal cord.

Thanks are due to Sir Trent Champion de Crespigny for permission to report this case and to Professor E. Weston Hurst of the Institute of Medical and Veterinary Science for his help in examining the histological sections.

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CONGENITAL COMPLETE HEART BLOCK

BY

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Congenital complete heart block is an uncommon condition. The two cases now recorded are of particular interest because they were diagnosed before birth. The diagnosis was confirmed postnatally by electrocardiogram.

Case 1. H., a male infant weighing 7 lb., was born on February 9, 1943, the first child of a twenty-five-year-old mother. During the mother's pregnancy the foetal heart sounds were never heard. Foetal movements were present from four-and-a-half months. Following rupture of the membranes seven hours twenty minutes before delivery, the foetal heart sounds became audible. The very slow rate was noted. It was regular, and the provisional diagnosis of complete heart block was suggested. At delivery the condition of the infant was good: there was no cyanosis. Auscultation of the heart disclosed no murmurs. The ventricular rate fluctuated from time to time and varied between sixty and seventy-six per minute. The infant was breast fed and made normal progress.

When five-and-a-half days old, two electrocardiograms and a skiagram were made. The first electrocardiogram showed an auricular rate of 176 per minute, a ventricular rate of 60 per minute, a constant P–R interval of 0·2 second, P waves upright in all leads, and the right axis deviation which is normally associated with the newborn infant. It suggested a 3 : 1 heart block. The second electrocardiogram showed a complete heart block. The auricular rate was constant at 188 per minute, while the ventricular rate varied between 60 and 71 per minute. The P–R interval varied between 0·1 and 0·28 second. The skiagram disclosed a globular heart shadow. The outline of the right auricle extended well out to the right. The supracardiac shadow was abnormally wide. The whole appearance suggested some structural cardiac abnormality, in all probability a degree of septal defect.

At the age of seventeen weeks a faint murmur could be heard. It was not well defined but could be heard best in the mitral region. An electrocardiogram and a skiagram were taken at this time. The former showed a persistence of the complete heart block. The auricular rate was 150 per minute and the ventricular rate approximately 52 per minute. The skiagram showed the cardiac outline to be unchanged.

Since the infant was born the ventricular rate has shown a downward trend. This is illustrated in the following table:

Age in days	Ventricular rate per minute
Birth	60–76
5	60–71
31	84
38	60
73	56
124	52

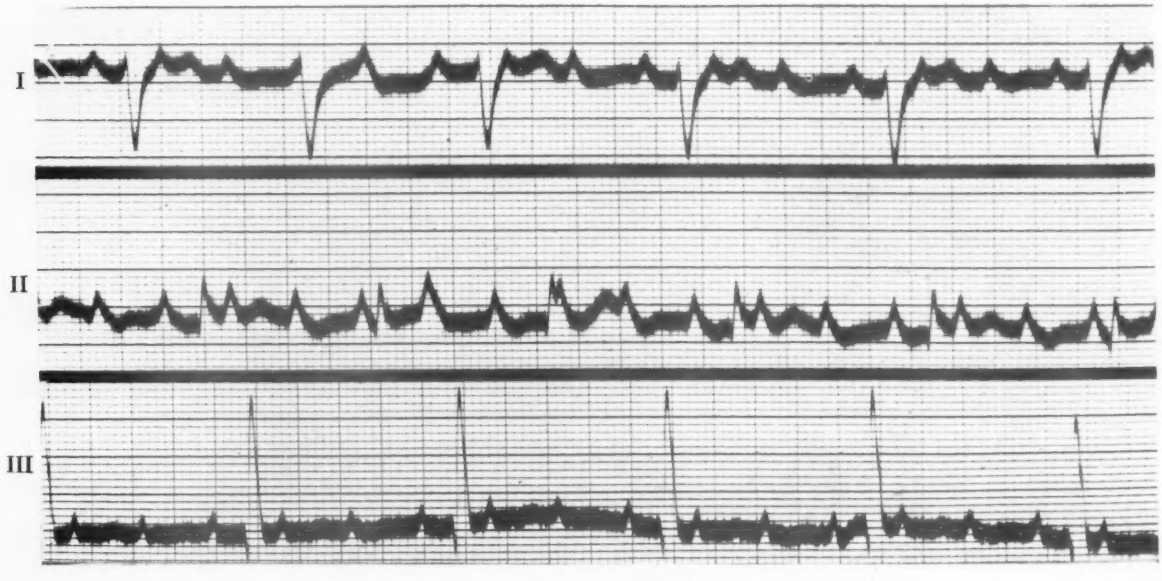

FIG. 1.—Case 1. Electrocardiogram at age 5½ days

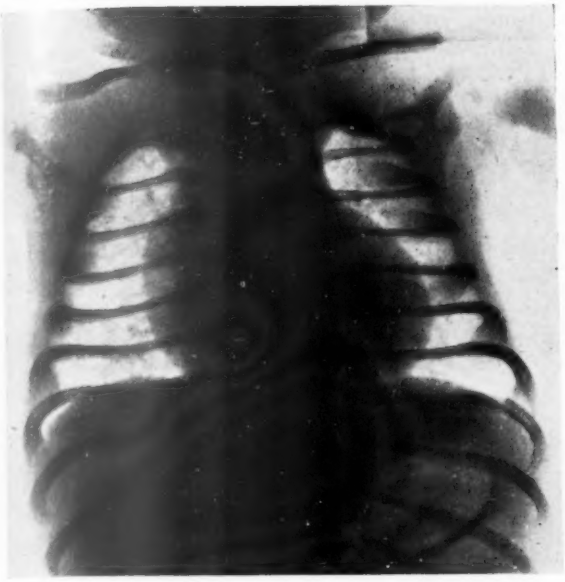

FIG. 2.—Case 1. Skiagram at age 5½ days

Cyanosis has been observed on only one occasion. It occurred during a fit of crying when the infant was 38 days old, and only amounted to a faint tinge round the mouth and eyes. The infant is now twenty-three weeks old and is clinically well.

Because of the occurrence of complete heart block in the infant, the mother's electrocardiogram was taken. This disclosed a bundle branch block, type IIa (Wilson). It is a matter for speculation whether this cardiac condition in the mother has had any relation to the occurrence of heart block in the infant. The mother, who had had diphtheria in childhood, is healthy at present. Several blood relatives of the mother, including her mother, have been examined but no other cases of heart block have been found.

Case 2. J., a female infant weighing 6 lb. 5¼ oz., born on March 28, 1943, the first child of a thirty-two-year-old mother whose Wassermann reaction was negative. Movements were felt at about five months. No foetal heart sounds were heard until about six-and-a-half months. They were then noted to be slow. At four-and-a-half weeks before delivery the rate was forty-five per minute and at four weeks before delivery it was forty-eight per minute. On the day before delivery the foetal heart was not heard. During the labour which lasted approximately twenty-two hours, it became audible but it was irregular. Rupture of the membranes disclosed that the liquor amnii was mixed with meconium. The labour was thereupon terminated by a forceps delivery. The infant was found to be in fairly good condition. There was no cyanosis and no cardiac murmur was detected. The cardiac rate remained unaltered.

Electrocardiograms were taken on the second and third days. They confirmed the diagnosis, already suggested, of a congenital heart block. The first electrocardiogram showed an auricular rate of 167 per minute and a ventricular rate of 83 per minute. The second electrocardiogram gave an auricular rate of 150 per minute and a ventricular rate of 68 per minute. In both the electrocardiograms the P waves were upright in all leads, while the P–R interval was variable. A skiagram which was taken at the age of two days showed a cardiac shadow extending further to the left than usual, and a narrow supracardiac shadow. A further skiagram which was taken a week later showed no change in the cardiac outline.

Unlike the findings in case 1, the ventricular rate has not shown the same tendency to decrease as the infant grows. The observations made are given in the following table:

Age in days	Ventricular rate per minute
2	83
3	68
9	76
11	68
24	72
38	72
52	70
66	72
115	70

The most recent electrocardiogram taken at the age

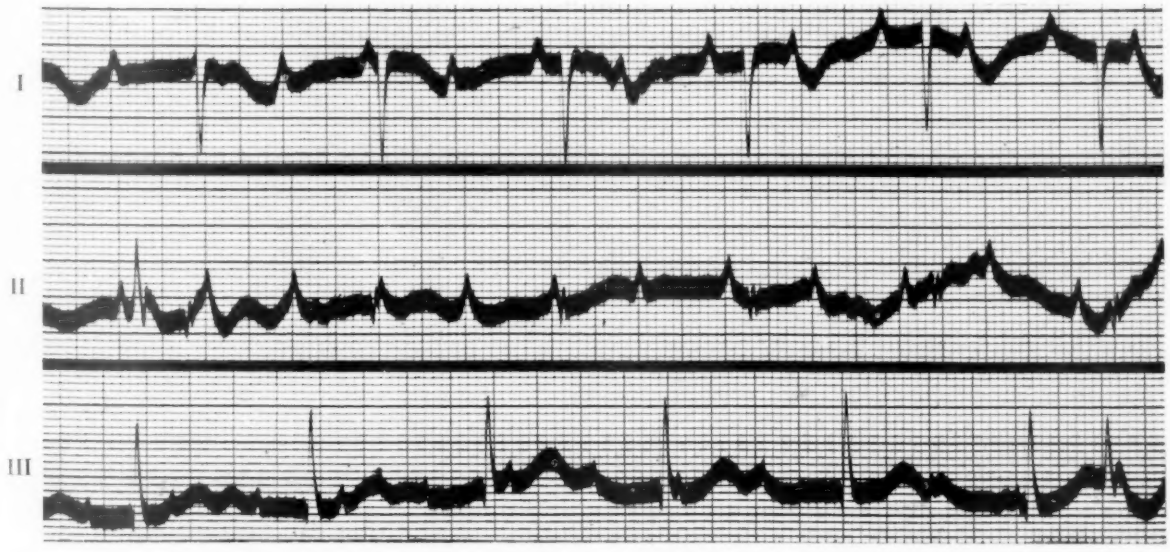

FIG. 3.—Case 2. Electrocardiogram at age 2 days

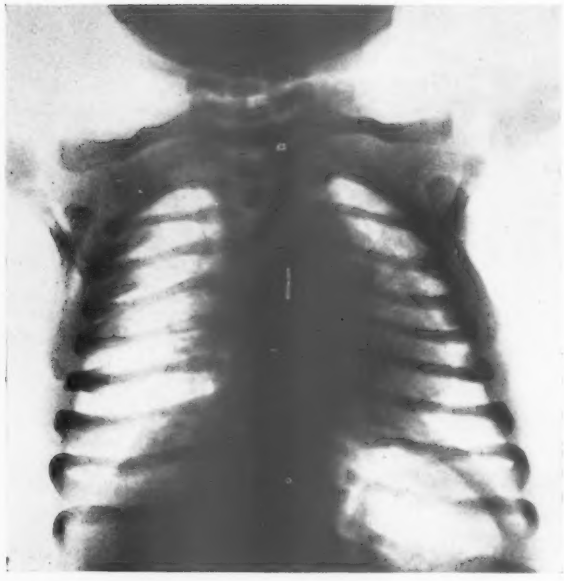

FIG. 4.—Case 2. Skiagram at age 2 days

of 8 weeks showed a persistence of the heart block. This breast-fed infant who is now sixteen weeks old has made satisfactory progress. The mother's electrocardiogram is normal.

Commentary

Nearly a hundred cases of congenital heart block have been recorded. Yater (1929) made an exhaustive survey of the literature to the end of 1928. Hays (1934) reported three cases and gave a resumé of the literature. Of recent years cases have been recorded by Currie (1940), Geiger and Hines (1940), Stein and Uhr (1942), Leys (1943), Peel (1943), and Campbell (1943). Though uncommon the condition is probably not rare.

Etiology. The cause of congenital heart block has seldom been ascertained, for few of the published cases have come to autopsy. Of those which have, the necessary histological investigation has been made in only two cases. One of these, recorded by Yater (1929), showed a complete separation of the auriculo-ventricular node from the auriculo-ventricular bundle. The other, a case of 2 : 1 heart block recorded by Wilson and Grant (1925), showed a well developed auriculo-ventricular node, but the conducting fibres coming from it were interrupted and broken up by fibrous tissue only to reunite and divide into right and left branches lower down. None of this fibrous tissue appeared to be inflammatory in origin. In this connexion it is interesting to note the case of a five-year-old child with heart block, reported by Armstrong and Mönckeberg (1911). In this instance a small primary tumour was found localized in the auriculo-ventricular node.

An examination of the electrocardiograms of the two cases now recorded shows the presence of a normal ventricular complex. This is in keeping with the cases already published. It demonstrates that the lesion must be in the course of the main bundle of His above the bifurcation, and close to the interventricular septum. This occurrence has almost certainly given rise to the statement that congenital heart block is due to the presence of a septal defect. Such a premise is not supported by the histological investigations of Yater and of Wilson and Grant. In the latter case indeed, although the block was only partial, there was an entire absence of the interventricular septum. Moreover, a case of congenital heart block has been recorded by Witt (1934) in which no septal defect was found at autopsy. There was a coarctation of the aorta. It is most unfortunate that no histological investigation was made in this case. The rarity of heart block in cases of interventricular septal defect has been explained on the ground that the usual site of a septal defect is anterior to the pars membranacea whereas the bundle of His runs behind it. Though this is certainly true it is no proof that congenital heart block is due to a septal defect. The case recorded by Heubner (1938) in which the block disappeared when the infant reached the age of eleven months does not support the theory of septal defect. Neither does the case reported by Geiger and Hines. In this case the block appeared to begin at between seventeen and nineteen hours before delivery when the foetal heart rate dropped from 136 per minute to 64 per minute. These two cases suggest an entirely different etiology: Heubner's case suggests a recovery from an intrauterine illness, and the case of Geiger and Hines suggests the supervention of an intrauterine illness, or perhaps a haemorrhage, causing interference with the conducting power of the fibres. The two cases now reported throw no light on the etiology of the condition. It is clear that when the opportunity arises, extensive histological examination of the conducting fibres of the heart should be made in cases of congenital heart block.

Diagnosis. The diagnosis of congenital heart block is more often made after the child has reached the age of two years than before it. When the amount of ante-natal work which has been done during the past twenty years is considered this is somewhat surprising. Cases of congenital complete heart block should be suspected prior to birth and either confirmed or disproved in the neonatal period. The two cases now reported bring the total number of cases of complete heart block diagnosed ante-natally to seven. A summary of the main features of these cases is given in tabular form (table 1).

The need for the early diagnosis in cases of congenital complete heart block is forcibly illustrated by the incident reported by Stein and Uhr. In this instance, a child aged three years was being operated upon for acute mastoiditis when the anaesthetist directed the surgeon's attention to the slow pulse. Naturally, the possibility of an intradural absce-

TABLE 1

CONGENITAL COMPLETE HEART BLOCK. CASES DIAGNOSED ANTE-NATALLY

Author	Sex	Slowest foetal heart rate	Slowest rate after birth	Time of ante-natal diagnosis	Duration of life	Remarks
Yater, 1929	m.	47	47	2 weeks	18 days	Marked cyanosis. Autopsy.
Witt, 1934	m.	44	44	2 months	75 days	Marked cyanosis. Autopsy.
Heubner, 1938	?	80	60	not given	Alive at 11 months	Block disappeared at this age.
Ottow, 1939	f.	32	52	24 hours	5 months	
Geiger and Hines, 1940 ..	f.	58	60	17 hours	5 months	
Thomson, 1943	m.	60	52	7 hours	23 weeks	
	f.	45	68	4½ weeks	16 weeks	

In all cases the diagnosis was confirmed by electrocardiogram.

was considered. Following upon a neurologist's negative report, the paediatrician to whom the case was then referred diagnosed a complete heart block.

In this case a low musical murmur was heard, probably due to a septal defect. A skiagram showed some right and left ventricular enlargement and the electrocardiogram confirmed the diagnosis. The auricular rate was 120 per minute and the ventricular rate 70 per minute.

Another instance in which a case of congenital heart block was overlooked is recorded by Campbell. He relates that a dental student who had a complete heart block contracted jaundice and was admitted to hospital. The slow pulse was remarked upon and the patient was demonstrated as having a bradycardia due to jaundice.

The possibility of Stokes-Adams seizure occurring in the case of heart block may explain some of those infantile or even ante-natal deaths in which at autopsy no cause for death can be found.

Summary

Two cases of congenital complete heart block, diagnosed ante-natally, are recorded. The need for histological examination of the heart in such cases is stressed. Attention is directed to the desirability of early diagnosis of congenital heart block.

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THE HEALING OF RENAL RICKETS

BY

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Little has been added to the knowledge of the treatment of renal rickets since the paper by Graham and Oakley (1938), and the reader is referred to their work for a summary of the previous literature of this condition. Whether or not in fact rickets is the principal bony lesion has been questioned by Langmead and Orr (1933). From a morbid anatomical study, they concluded that osteitis fibrosa was the outstanding pathological change in the bones, and attributed this to osteoclastic activity caused by excessive parathyroid function. They were able to demonstrate the presence of hypertrophy of the parathyroid glands. Their view has received support in America from such authorities as Park and Eliot (1942), and Hamilton (1940) who considers the hyperparathyroidism to be secondary, and called into being in order to rectify the low blood calcium level so often present in chronic nephritis. It is not the purpose of this communication to discuss the underlying pathological process in the bones, although it may be pointed out that so-called renal rickets may occur with a normal blood calcium, as in the cases reported by Karelitz and Kolomoyzeff (1932), but to place on record the history of a boy with chronic nephritis whose bone changes, characteristic of renal rickets, underwent such complete healing during the eight months prior to his death that histological examination of a radius showed neither rickets nor osteitis fibrosa, ossification appearing to be proceeding in an orderly manner.

Case history

The patient, a boy aged 4½ years, was seen in consultation on April 2, 1942. He was the fifth and youngest child, the parents and older children being healthy. From birth (the newborn period having been apparently uneventful), at intervals of six months, the patient had been subject to attacks of feverishness, vomiting, and drowsiness lasting up to a week, and between attacks he was noticeably listless, suffered from thirst which would cause him to wake twice each night for a drink, and passed large quantities of urine which was at times offensive. He had learned to walk, but during the previous four months bowing of the legs had rapidly progressed, and for the last fortnight he had been too weak to stand.

Examination showed him to be of short stature, and weighing only 31 lb. Although cooperative, he was very apathetic. His mouth and skin were dry, and he appeared severely anaemic. The heart was not enlarged, and the systolic blood pressure was 70 mm. Hg. Apart from the scar of an operation for inguinal hernia, the abdomen was normal, and the kidneys could not be felt. The tonsils appeared healthy. There were no retinal changes. An obvious feature was the coarse tremor of the trunk and limbs during voluntary movements. The boy gave a positive Chvostek sign of latent tetany, but no evidence of active tetany. Signs of rickets abounded; the epiphyses at the wrists and ankles were swollen, the costochondral junctions were beaded, Harrison's sulcus was present, and the left leg was bowed inwards to form a pronounced genu valgum while the right showed an equally severe genu varum. The urine was cloudy, specific gravity 1008, and contained a thin cloud of albumin and a few pus cells; culture gave a growth of B. coli.

On the above evidence, a diagnosis was made of renal fibrosis with renal rickets and chronic uraemia. Because of the presence of urinary infection, it was considered that the fibrosis of the kidneys might be associated with some congenital abnormality of the urinary tract, but an attempt to obtain a pyelogram following the intravenous injection of 12 c.c. of perabrodil failed because the kidneys were unable to excrete the drug sufficiently rapidly to give a high enough concentration.

Treatment. The patient was admitted to hospital on April 6, 1942. On admission the serum calcium was 4·6 mgm. per 100 c.c., and the absence of active tetany in spite of so low a calcium level was considered to be due to the acidosis accompanying the chronic nephritis. The alkali reserve was considerably reduced. It was decided to attempt the relief of the uraemia by giving alkalis, but in case this should precipitate active tetany, calcium gluconate (30 grains thrice daily) was given, and this dose was maintained until within a week or so of death. Alkali was given in the form of sodium bicarbonate and sodium citrate, 10 grains of each every four hours. There was some difficulty in getting the child to tolerate this amount, and at first it caused vomiting, but by starting with smaller doses and gradually increasing them, the full dose of 100 grains daily was attained, and persisted with for four months. The dose was then lowered to 60 grains daily for another two months, when, in the face of progressive uraemia and early nephritic

oedema, the alkaline treatment was abandoned. It had incidentally served the purpose of keeping the urinary infection at bay.

In the hope of forcing up the blood calcium, and thus possibly leading to an improvement in the rickets, large amounts of vitamin D were given: 10,000 I.U. of calciferol were given twice a day from the middle of April until the end of October. The effect on the blood calcium was disappointing, the child remaining hypocalcaemic throughout (see table 1), but during this period the bones steadily healed until eventually the x-ray picture became virtually normal. The risk that such big doses of vitamin D, together with calcium orally, might lead to calcification in the soft tissues, was appreciated, and a watch was kept on the kidneys and medium-sized arteries by repeated x-ray examinations, but metastatic calcification did not appear.

Throughout the child's stay in hospital, anaemia was persistent and severe. Monthly blood counts showed the red cell count varying between 2 million and 2½ million per c.mm., the haemoglobin hovering between 40 and 45 per cent. The leucocytes ranged between 7000 and 9000 per c.mm., the polymorphs gradually dropping from 74 per cent. in May to 44 per cent. in August. Treatment of the anaemia by a proprietary iron preparation, to which was later added 1/200 grain copper sulphate, made no impression on the blood count. The kidney function was so defective that blood transfusion was held to be contra-indicated.

The blood calcium, blood phosphorus, phosphatase, and blood urea were repeatedly estimated, and are presented in the following table :—

TABLE 1

Date	Blood calcium: mgm. per 100 c.c. serum	Blood phosphorus: mgm. per 100 c.c. serum	Phosphatase: units	Blood urea: mgm. per 100 c.c. serum
9.4.42	4·6	8·9	62·8	410·0
7.5.42	7·7	—	53·0	150·0
18.6.42	6·8	10·3	62·3	190·0
23.7.42	6·8	13·8	54·3	294·0
23.8.42	6·8	—	—	249·0
15.9.42	5·4	—	—	236·0

Course. A week after admission to hospital, and coincident with the beginning of alkaline therapy, the boy went into an attack of acute uraemia, but recovered under treatment by gastric and colonic lavage. His general condition then improved slightly, and as serial x-ray examinations showed improvement in the degree of rickets, splints were applied to try to correct the deformity of the knees, and special boots were on order in the hope that he might be able to walk. However, he never attained this degree of improvement, remaining in bed throughout his stay in hospital. A month before he died, puffiness of the face appeared, and from then oedema became progressively more severe and widespread, and was accompanied by ascites. Eventually, after eight months in hospital, he died in uraemia.

Post-mortem examination. At post-mortem examination, both kidneys were much contracted, and their surface granular. The left renal pelvis was thickened and dilated into a small hydronephrosis; the right renal pelvis was normal. The parathyroid glands were not examined. The lower end of one radius was examined; the shaft of the bone appeared well calcified, the calcification extending right down to the epiphyseal line, which was straight and even.

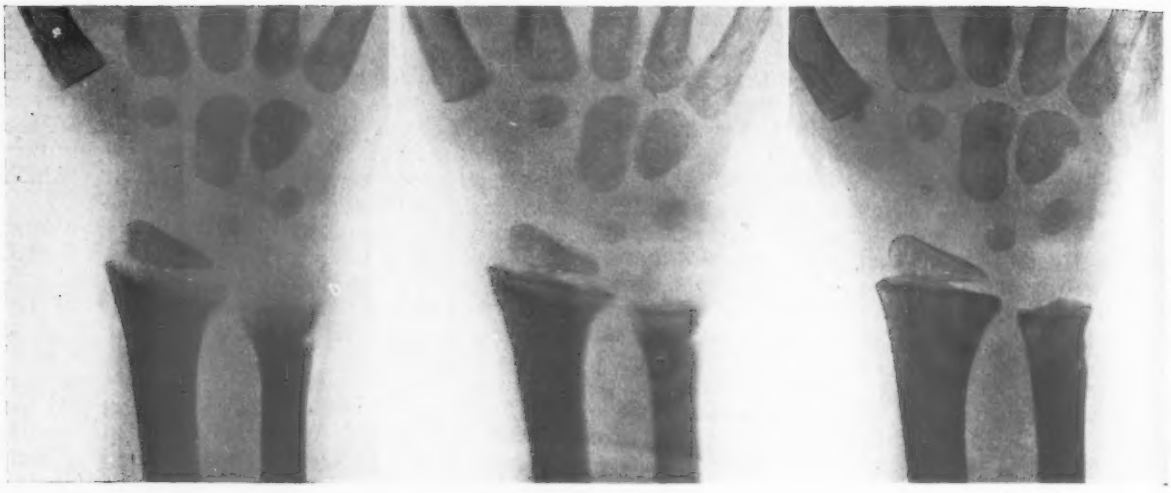
Histological examination of the kidney and radius was kindly carried out by Dr. F. M. Creed, and his report was as follows:—'The kidney is badly disorganized. A large proportion of the glomeruli are completely hyalinized, others show various stages in the process. All the glomeruli are comparatively bloodless. In a few there is a dilated glomerular space, but for the most part the tuft fills the capsule and is partially or wholly adherent to it. In many places there has been complete atrophy and disappearance of tubules, elsewhere dilated tubules persist. Interstitial tissue is enormously increased and there is much infiltration with lymphocytes and plasma cells. The vessels show great intimal thickening, often nearly or quite occluding the lumen, and there is medial hypertrophy. The bone shows no evidence of osteitis fibrosa, nor of rickets, and ossification appears to be proceeding in an orderly manner.'

X-ray appearances. In addition to repeated x-ray examinations of the soft tissues in order to detect metastatic calcification, which, as has been stated, did not arise, the wrists and ankles were x-rayed once a month. The first x-ray examination in April, 1942, showed the typical appearance of severe renal rickets; successive films revealed steady healing, until by October, 1942, healing seemed to be complete. The accompanying illustration (fig. 1 and 2) show these stages.

Discussion

Discussion turns on the mechanism which led to healing of the bones in the face of a deteriorating renal lesion. Parsons (1927) has stated that in renal rickets the bones are in a state of flux between alternate healing and relapse, and that this is dependent upon the falling and rising of the blood phosphorus, coincident with the renal function being in a phase of improvement or retrogression; and that in this way healing of the bones may occur in the absence of any particular therapeutic measure. In the case here recorded, during the first three months of treatment, the blood phosphorus estimations showed a steady rise, and in spite of that, the x-ray examination showed progressive improvement in the bony condition, from which it would seem that the healing of the bones in this particular case cannot be explained by the view expressed by Parsons.

Graham and Oakley (1938) treated their two cases with sufficient alkali to maintain a normal alkali reserve, giving the equivalent of 20 gm. and 12 gm. of sodium bicarbonate daily to their respective cases, and they offer an explanation of how this treatment could lead to healing of the bones; but as their patients also had 6000 I.U. vitamin D daily, they were unable to decide whether the



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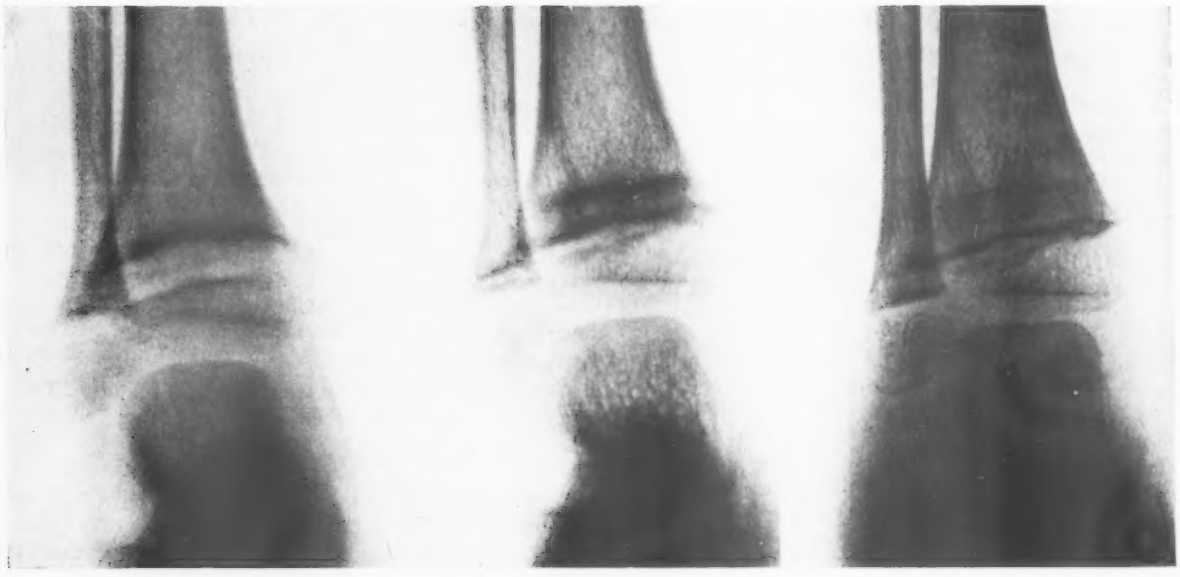

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FIG. 1 and 2.—X-ray pictures of wrist (fig. 1) and ankle (fig. 2) showing stages in the recovery of renal rickets.

alkali or the vitamin had been responsible for the recovery. The same dilemma arises in the case here described, although the amount of alkali (100 grains daily for four months and 60 grains daily for a further two months) was much less than that given by Graham and Oakley, while the amount of vitamin D was more than three times as great. To give calcium by mouth would, of itself, be unlikely to improve the state of the bones, although it may possibly have tended to prevent the calcification of the bone ends taking place at the expense of the calcium in the shafts. In spite of the high dose of vitamin D, calcification of the soft tissues did not occur, presumably because a state of hypercalcaemia was never attained.

The two noteworthy features of the case here recorded are the degree to which the bones recovered, and that this occurred in the face of a high and rising blood phosphorus value and a persistent hypocalcaemia.

Summary

The case of a boy aged 4 years with chronic nephritis and renal rickets is recorded, in whom the bones underwent complete healing under treatment with alkalies, calcium and large amounts of vitamin D. The recovery in the bones is regarded as not fortuitous, but it is not possible to decide whether this result came about because of one therapeutic measure alone, or because of the combined therapy.

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SPONTANEOUS PNEUMOTHORAX, MASSIVE COLLAPSE, AND SUBCUTANEOUS EMPHYSEMA COMPLICATING ASTHMA

BY

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Subcutaneous emphysema or spontaneous pneumothorax in association with asthma is a rare complication and the combined condition is even more rare, only one case report being found in the literature. For these three conditions to be present in association with massive collapse of the lung is, in all probability, unique.

Subcutaneous emphysema complicating asthma. Rosenberg and Rosenberg (1938) report the condition in a child aged three years and could only find seventeen similar cases in the literature. These occurred in the age period 3 to 38 years, eleven cases occurring in the first two decades. The duration of the emphysema was two days to three weeks, and although several were very ill there were no

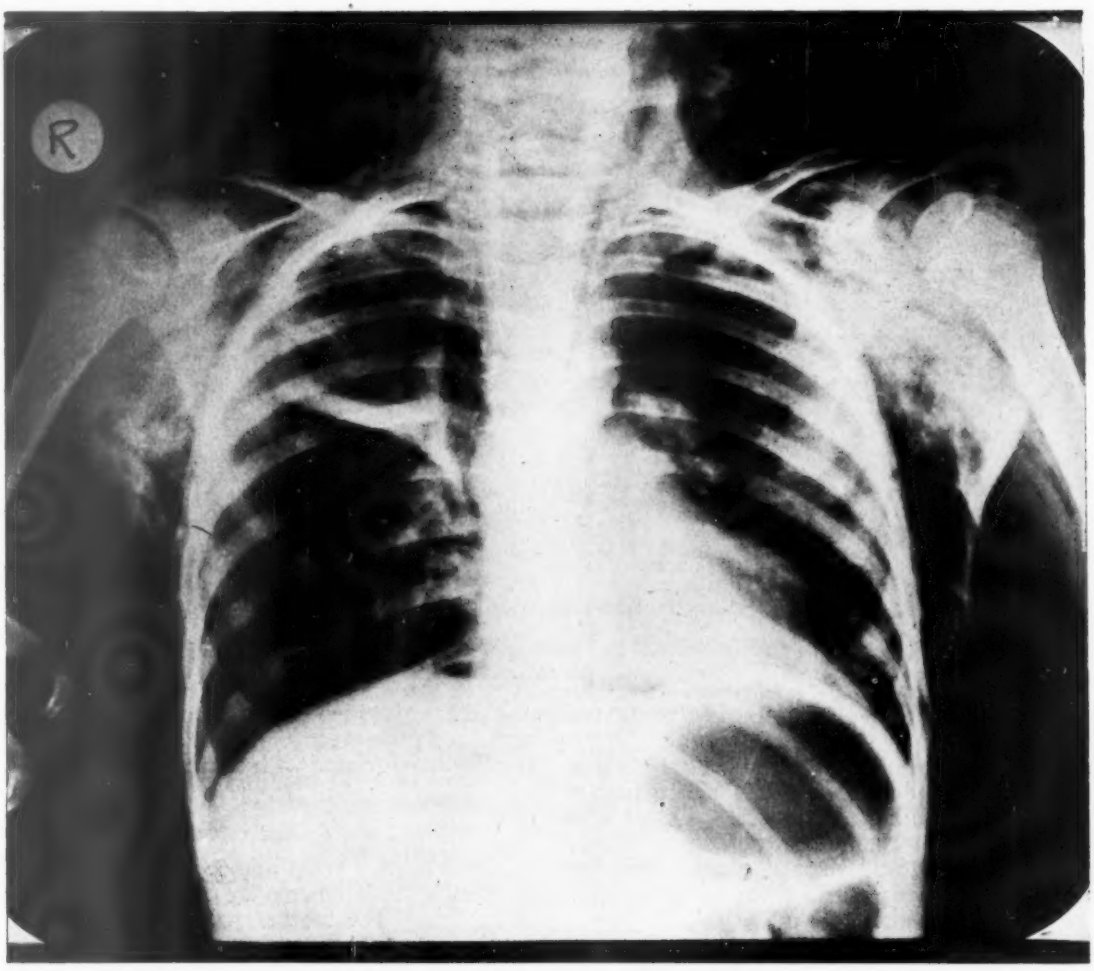

FIG. 1.—Second day of first asthmatic attack showing subcutaneous emphysema; displacement of heart to the left with collapse of left lower lobe; V-shaped shadow in right upper lobe probably inflammatory.

deaths and no recurrences. Macklin (1939) produced the condition in cats by distending the lungs with air through a catheter in a bronchus. It was seen on section that the alveoli had ruptured in several minute spots and the escaping air had tracked along the interstitial tissue of the pulmonary vessels to the hilum. In doing so it tends by pressure to occlude the vessels and cause circulatory embarrassment. From the hilum the air either tracked up to the neck and face, downwards to retro-peritoneal tissues and legs, across to the heart, or through into the pleural cavity producing a spontaneous pneumothorax. The latter may bring about a cure by closing the holes in the ruptured alveoli.

Spontaneous pneumothorax complicating asthma is possibly a rarer occurrence than subcutaneous emphysema, but a more serious one. Castex and Mazzei (1938) review the literature of twelve cases. The age period (11 to 59 years) is higher than for subcutaneous emphysema and three died, giving a mortality of 25 per cent.

Subcutaneous emphysema and spontaneous pneumothorax in asthma. Elliott (1938) reports the condition in a woman aged 46. Emphysema developed at the onset of the attack, and two days later partial pneumothorax was discovered by x-ray examination on the right side. He could find no other case report of this condition.

Massive collapse of the lung in association with asthma is a comparatively common occurrence, it is usually transient and can be accounted for by sticky secretion being held up in a narrowed spastic bronchus with absorption of air and consequent collapse in the part of lung supplied by that bronchus. As the attack passes off the bronchus dilates, the secretion becomes more fluid and is coughed up and the lung re-expands.

Spontaneous pneumothorax with massive collapse of the lung. Cummings (1935) reports a case in a child aged nine months following pneumonia with complete recovery, but no report of this condition associated with asthma can be found.

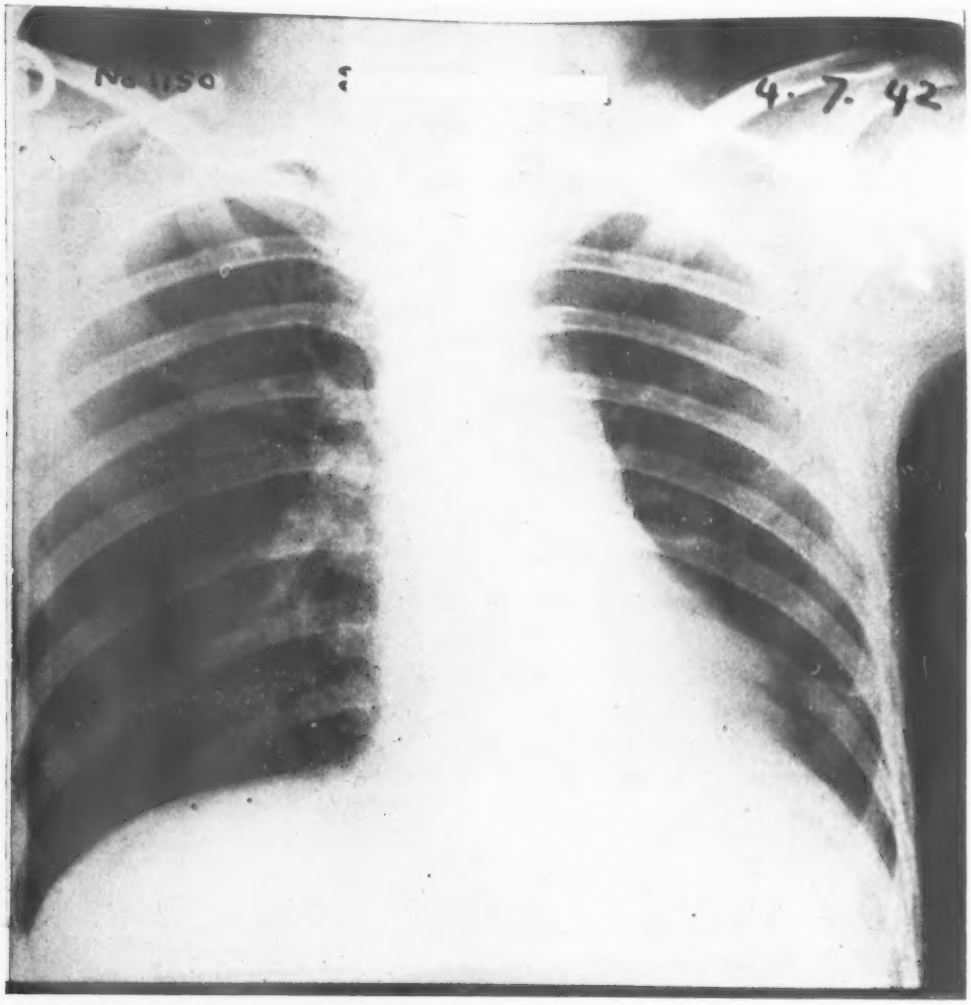

FIG. 2.—One week after first asthmatic attack. Subcutaneous emphysema subsided; collapse of left lower lobe persists.

Case report

A girl aged 4 years and 2 months was admitted to hospital as an emergency on June 28 in an attack of asthma. The mother stated that the child had developed a cold three days previously but had only been breathless and wheezy for one day. On the morning of the admission swelling of the neck was noticed for the first time. The child had suffered from severe asthmatic attacks every four to six

weeks since ten months of age and earlier in the year had received a course of injections of mixed inhalants plus 20 per cent. pollens, as skin tests showed her sensitive to pollens.

PREVIOUS ILLNESSES. She had pneumonia at 18 months with whooping cough, since when her asthma had been worse. There was no eczema in infancy.

FAMILY HISTORY. No one suffered from hay fever or asthma, but the mother had migraine.

PRESENT STATE. On admission she looked ill, was cyanosed and dyspnoeic, but not wheezing. Temperature was 99·8 F., pulse 144 and respiration 34 per minute. There was subcutaneous emphysema extending around the neck, on the face, over the chest, abdomen and thighs. On examination of the chest the heart appeared to be central, the breath sounds were harsh and rhonchi heard over both lung fields, but subcutaneous emphysema prevented the detection of râles.

X-RAY OF CHEST (fig. 1) showed extensive subcutaneous emphysema, the heart was displaced to the left with a shadow behind the left border suggesting collapse of the left lower lobe. The left hilar glands were enlarged. In the right upper zone there was a V-shaped shadow pointing towards the hilum.

TREATMENT. She was given adrenalin 2 minims and nepenthe 5 minims, and put in an oxygen tent. Air was aspirated from the pectoral region, but as this caused more distress than relief it was discontinued.

PROGRESS. Although her respiration had risen to 47 a minute the next day, her general condition had improved and she was removed from the oxygen tent. During the next twelve days the subcutaneous emphysema slowly subsided and completely disappeared and the child was transferred to the Base Hospital. Further investigations showed her tuberculin reaction (Mantoux 1/1000) was negative.

The adventitious signs in the chest disappeared, but the percussion note remained dull at the left base. X-ray examination of the chest on July 4 (fig. 2) shows the heart still displaced to the left with an opacity behind suggesting persistence of the left lower lobe collapse confirmed in the lateral x-ray. The right upper zone shadow had disappeared.

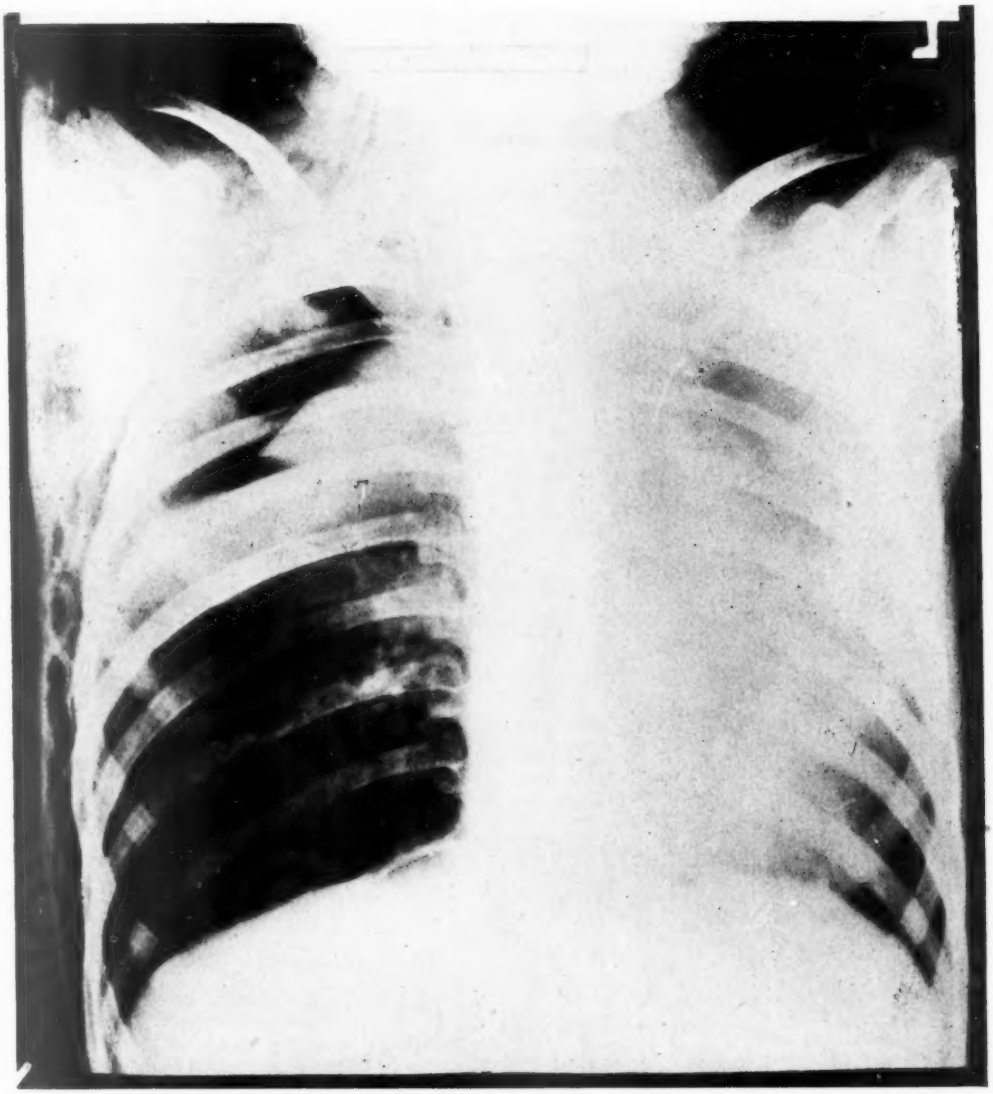

FIG. 3.—Second day of second asthmatic attack showing heart in left chest with massive collapse of left lung; localized collapse of right upper lobe with spontaneous pneumothorax.

She remained fairly well until July 10 when she developed a hard cough, was 'off colour' in the afternoon and refused her tea. The temperature was normal, but respirations had risen to 36. On examination of the chest the forcible apex beat had moved to the left and was now in the mid-axillary line. The left side of the chest was dull to percussion with a poor air entry; on the right side, the percussion note was normal, but expiration was prolonged and scattered rhonchi were heard on both sides. By 8.30 p.m. she was much more dyspnoeic and examination of the chest now showed hyperresonance over the right lung. One hundred cubic centimetres of air was aspirated from the eighth right intercostal space behind, no more being obtainable. This made the child worse, so she was placed in an oxygen tent. In spite of the lung findings the child appeared to be in a severe asthmatic attack, so she was given adrenalin hydrochlor. (1/1000) 10 minims (one minim a minute) and atropine sulphate, 1/100 grain. This produced considerable relief. At midnight the condition was still serious, and the chest signs showed little change, the percussion note on the right side was more hyperresonant at the right apex and the breath sounds were very faint. Aspiration of air was repeated, this time in the second interspace anteriorly and 630 c.c. obtained. During this process the apex beat moved in an inch. She was now given nepenthe 4 minims by mouth and had a fair night in the oxygen tent.

When seen at 9 a.m. the next morning (July 11) she was very restless, the chest signs showing no significant change. She was given another dose of nepenthe, 4 minims. At mid-day, after a good sleep, she suddenly sat up and said she was hungry, she looked very much better and ate a good meal, although still dyspnoeic. At this stage an x-ray picture of the chest was taken (fig. 3). It shows the heart displaced into the left chest, and practically no aeration of the left lung except at the costophrenic angle. In the upper part of the right chest there is a localized spontaneous pneumothorax producing a localized collapse of the adjacent lung.

In two days' time her dyspnoea had disappeared and the chest signs were returning to normal.

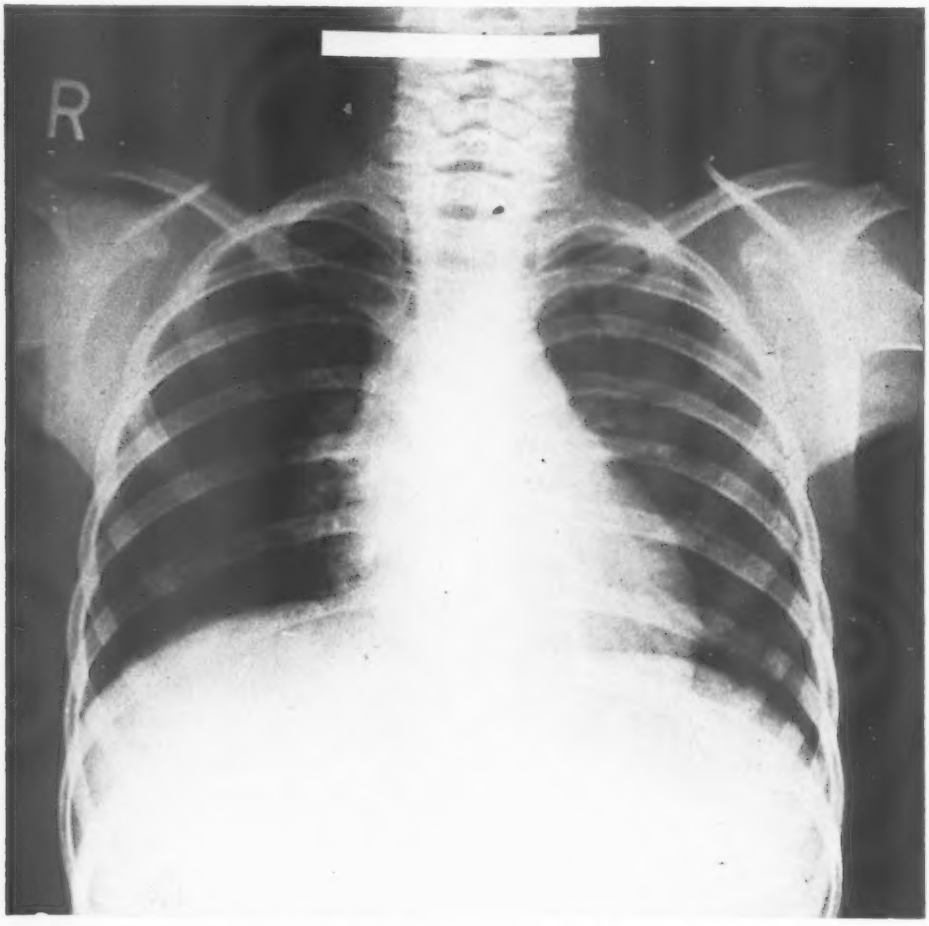

FIG. 4.—Nineteen days after second asthmatic attack showing a normal chest x-ray.

On July 20 a further x-ray showed the heart practically central and the left lung to be fully expanded. The localized right spontaneous pneumothorax was smaller. On July 28, x-ray examination of the chest was normal (fig. 4) and the child was discharged home on August 1. She had only had two mild attacks of asthma since and no recurrence of the subcutaneous emphysema, spontaneous pneumothorax or collapse.

Discussion

A possible explanation for the sequence of events occurring in this remarkable case is as follows. On June 25 a nasopharyngeal infection developed and spread to the right upper lobe of the lung

producing a mild inflammation. Two days later an asthmatic attack occurred causing rupture of alveoli in the inflammatory area of the right upper lobe. Air tracked along the interstitial tissue of the lung to the hilum, up the mediastinum to the neck, face, chest, abdomen and thighs. X-ray examination at this time suggests an associated collapse of the left lower lobe. The subcutaneous emphysema was slowly absorbed, but the collapsed left lower lobe persisted. On July 10 (fifteen days from the first symptom) a second attack of asthma developed resulting in accumulation of mucus in the left upper lobe bronchus producing sudden collapse of the left upper lobe. This catastrophe combined with the already collapsed left lower lobe produced a rapid shift of the heart and mediastinum to the left, resulting in rupture of recent adhesions in the right upper lobe. The recently sealed air leak was reopened, this time into the pleural cavity, producing a localized spontaneous pneumothorax.

Summary

A case is reported of a girl aged 4 years and 2 months who showed the combined features of asthma, subcutaneous emphysema, collapse of the left lung and spontaneous pneumothorax in the right chest, with recovery. This is probably a unique phenomenon.

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